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Organo Ufficiale della Società Italiana di Psicopatologia

JOURNAL OF PSYCHOPATHOLOGY

GIORNALE DI PSICOPATOLOGIA

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Contemporary psychopathology
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Founders: Giovanni B. Cassano, Paolo Pancheri

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Chapters from books or material from conference proceedings:
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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).

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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.

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3. Articoli brevi: questo spazio è riservato a brevi comunicazioni relative a dati clinico-sperimentali e a dati preliminari di ricerche in corso di particolare interesse. Il testo non dovrà superare i 20.000 caratteri spazi inclusi comprese tabelle e/o figure e una decina di voci bibliografiche.

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Toward a new psychopathology

Psychiatry, ill-defined as it is at present, still bases its practice, education and research on a number of paradigms that have been formulated in the last century. Many of these have eroded [1] and are likely to require a reformulation or replacement by new paradigms [2]. The changes in society and medicine that have contributed to the need to replace paradigms have already been reported and described [3 4]. In this special issue of the Journal of Psychopathology, we aim to present and discuss new forms of psychopathology and new psychiatric disturbances, which represent the consequence of the health, cultural, technological, economic and scientific changes that have recently occurred in society. In particular, social crisis and modernisation have significantly modified boundaries of psychopathology [5]; too often psychiatrists are called to deal with mental health problems, which are not proper mental disorders, but abnormal reactions to adverse life events or to external and internal stressors [4]. The new expressions of psychopathological problems, which are due to the above changes, are generating diagnostic and therapeutic difficulties for clinicians and other mental health professionals [6 7], which make the rediscovery of psychopathology one of the top priorities for psychiatric training and practice [8 9].

In this issue of the Journal of Psychopathology, several papers deal with these new expressions of psychopathology, taking into account a broad perspective from epidemiology and diagnostic features to treatment options. In particular, the introductory paper of this issue has been entrusted to Prof. Giovanni Stanghellini with the case of gender dysphoria, which is considered a paradigmatic example of the psychopathology of the present. The second paper deals with the role of society and modernisation on psychopathology, going beyond the DSM-5 [10]. The link between molecular neurobiology and phenomenological psychopathology has been investigated in the paper on schizophrenia, giving the way to a new wave of collaborative research between psychopathologists and neuroscientists. The other classic psychiatric syndromes, such as depression, bipolar disorder, anxiety disorders and obsessive-compulsive disorder, are considered in light of recent psychopathological changes that have been made to the DSM-5 [11] and that are likely to modify psychiatric practice. New forms of psychopathologies, such as those related to dysfunctional use of the Internet, pathological gambling and other behavioural addictions, as well as the effects of new psychopathological phenomena induced by novel psychoactive substances, all find their appropriate place in this issue. A search for a common psychopathological ground of the new forms of (proposed) eating disorders, and of the many somatic symptom disorders, is proposed in the respective papers. The reported psychopathological perspectives on suicide attempters and migrants will help us to better understand the clinical characteristics of groups who are at high-risk of developing psychiatric disorders. Finally, a look into postmodern society from a psychopathological viewpoint is made by taking into account clinical, anthropological, legal and social considerations.

All papers in this issue have been written by Italian and international expert clinicians and researchers in the field, making this special issue the first attempt to balance Italian research and practice with those from US, UK, Denmark, Germany, Spain, Canada, Portugal and Japan. We found this issue extremely stimulating for our every day practice, since many of our new patients are described herein, and many questions of our students are answered.

We are proud to bring to the attention of the readers of the Journal of Psychopathology this update on new psychopathological aspects of the various mental disorders, and we hope that the readers will found it as stimulating as we did.

Andrea Fiorillo[1] (Guest editor), Alessandro Rossi[2] (Editor)

[1] Department of Psychiatry, University of Naples SUN, Naples
[2] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy

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Psychopathology of the present: the case of gender dysphoria

G. Stanghellini

G. d'Annunzio" University, Chieti, Italy; "D. Portales" University, Santiago, Chile

Summary

Dialectic, person-centred psychopathology acknowledges the vulnerability constitutive of human personhood. It assumes that the person is engaged in trying to cope and make sense of disturbing experiences stemming from the encounter with alterity. Each patient, urged by the drive for intelligible unity of life-construction, with their unique strengths and resources, plays an active role in interacting with these experiences. The product of this yearning for meaning can be either the construction of a new identity, or vice versa mental symptoms. Mental symptoms are the outcome of a miscarried attempt to make sense of one's disturbing experiences.

The crisis of the dialogue of the person with an alterity that inhabits one is at the heart of mental disorders. So-called 'gender dysphoria' is an exemplary case study of this interrupted dialogue between the person and oneself. In gender dysphoria, the person suffers from a marked incongruence between his or her experienced gender and the assigned sex, for instance, a person living with a man's body who struggles to shape his body as a female body. This provides an illustration of the vulnerable duplicity that is inherent in the human condition and of the emergence of symptoms as the cypher of a miscarried dialogue with alterity. In gender dysphoria, the dialectics between one's sexual body as alterity and one's identity comes to a stop. Dysphoria, which is an unpleasant mood state characterised by uneasiness, irritability, restlessness and despair, is the core symptom of this disorder.

Key-words

Autonomy • Dialogue • Gender dysphoria • Person-centered psychopathology • Phenomenology

Introduction

We are a dialogue: of the person with oneself, and with other persons. Mental disorder is the interruption of this dialogue through which we strive to build and maintain our personal identity and our position in the world. The crisis of the dialogue of the person with the alterity that inhabits him/her, and with the alterity incarnated in the other persons, is at the heart of mental disorders. So-called "gender dysphoria", that is, the pathological feeling of uneasiness a human may experience when he/she is at odds with ones sexual body, is an exemplary case study of this interrupted dialogue between the person and oneself in the general framework of the psychopathology of the present.

Human existence is a yearning for unity and identity. Yet, this attempt is unfulfilled in the encounter with alterity, that is, with all the powers of the involuntary: unwitting drives, uncontrolled passions and automatic habits leading to unintended actions, as well as needs, desires, impulses and dreams. Finally, alterity can be encountered in one's body, the impersonal and pre-individual element that is to each of us the closest and the most remote at the same time [1]. One may feel forced to live in the intimacy with an extraneous being – one's own body, that is, the a priori determined Whatness of Who we are. One may feel stuck with one's sheer biological body, its facticity, the raw material that constitutes the unchosen and sedimented part of one's being and sets the boundaries of one's freedom. Who stems from the fragile, complex and obscure dynamics of the voluntary efforts to make sense of the involuntary What that is inherent in human personhood.

All this generates feelings of estrangement. Mental symptoms can be read as miscarried attempts to struggle for a sense of reconciliation to heal the wounds of disunion. Only as I recognise the alterity that inhabits me as an incoercible datum can I begin to use it in my service. Care is an attempt to re-establish such a fragile dialogue of the soul with oneself and with others. Such an attempt is based on one pillar: a dialectic, person-centred understanding of mental disorders. Its aim is to improve therapeutic practice in mental healthcare.

Dialectic, person-centred psychopathology

The dialectic understanding of mental disorders acknowledges the vulnerability constitutive of human personhood. It assumes that the person is engaged in trying to cope, solve and make sense of new, disturbing, puzzling experiences stemming from an encounter with alterity.

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Each patient, urged by the drive for the intelligible unity of his/her life-construction, with unique strengths and resources, plays an active role in interacting with these experiences. The product of this yearning for meaning can be establishing a new identity, or vice versa mental symptoms. These are the outcomes of a miscarried attempt to make sense of one's disturbing experiences [2]. Mental symptoms are not simply the direct outcome of some kind of dysfunction or of a "broken brain". A person's symptom is not generated as such – as it was the case with Minerva, who sprang fully armed from Jupiter's head. Rather, it is the outcome of the need for self-interpretation that each person has with respect to his/her encounter with alterity, that is, with challenging, unusual or abnormal experiences.

The psychopathological configurations that human existence takes on in the clinic are the outcome of a disproportion between the person and the encounter with alterity, and with the disturbing experiences that stem from it. The person is engaged in trying to cope, solve and make sense of the basic disturbing experiences stemming from the clash with alterity. Alterity is made manifest as a kind of estrangement from oneself and alienation from one's social environment. Faced with new, puzzling experiences, the person tries to make sense of them. The attempt to achieve a self-interpretation of perplexing experiences characterizes the person's attitude, alongside a comprehending appropriation, that is, the constant search for personal meaning.

The encounter with alterity may offer the advantage from which a person can see oneself from another, often from a radically different and new perspective. Thus, otherness kindles the progressive dialectics of personal identity. Narratives are the principal means to integrate alterity into autobiographical memory, providing temporal and goal structure, combining personal experiences into a coherent story related to the self. Yet, the encounter with alterity is also the origin of mental symptoms. The production of a symptom is the extrema ratio for alterity to become discernible. The symptom is the last chance for the person to recognise alterity in oneself. The patient, as a self-interpreting agent who interacts with her anomalous experiences, "works through" them in such a way that they become symptoms. Psychopathological symptoms are the outcome of miscarried attempts to give a meaning to distressing experiences, and to explain and cope with them.

The main difference between this person-centred understanding of mental disorders and a reductionist model is that in the latter the patient is conceived as a passive victim of ones symptoms, whereas the former attributes to the patient an active role in shaping symptoms, course and outcome. Urged by the painful tension that derives from the drive for the intelligible unity of life-construction [3], each patient, as a "goal directed being", plays an active role and stamps his/her autograph onto the raw material of basic abnormal experiences. When a clinical syndrome emerges, the line of the pathogenic trajectory is the following: 1) a disproportion of alterity and the person's resources for understanding, of emotions and rationality, of pathos and logos, of otherness and selfhood bringing about a disturbing metamorphosis of self and world experience; 2) a miscarried auto-hermeneutics or self-interpretation of one's abnormal experiences and of the transformations of the life-world that they bring about; 3) the fixation in a psychopathological structure in which the dialectics between the person and alterity gets lost.

This person-centred, dialectic approach helps us to see the patient as a meaning-making entity rather than as a passive individual [4]. The patient "can see himself, judge himself, and mould himself" [5]. His attempts at self-understanding are not necessarily pathological and are potentially adaptive.

This approach contains a theoretical framework and practical resources for understanding the diversity of psychopathological structures, including symptom presentation, course and outcome as a consequence of the different ways patients seek to make sense of and value the basic changes in self and world experiences. It also contains a framework for engaging with human fragility through person-centred, dialectic therapy.

The person-centred, dialectic approach involves two fundamental attitudes to mental illness:

- it is a therapeutic approach that acknowledges the subjective fragility constitutive of human personhood;
- it also insists, however, on our responsibility to care for this fragility for becoming the person that we are.

To become the person that we are, we must become aware of what we care about because being a person is to take upon oneself the responsibility involved in what one cares about. This approach is sensitive to the constitutional fragility of "who" and "what" we are and thus conceives psychopathological structures as the result of a normative vulnerability intrinsic to being a human person. It insists that to help a suffering person is to help that person to responsibly deal with the obscure entanglement of freedom and necessity, the voluntary and involuntary, and with ones sufferings as the result of the collapse of the dialectic of selfhood and otherness.

What is a symptom?

Handbooks usually present a list of phenomena that should be assessed and treated. By doing so, they establish a system of relevance concerning what should attract the clinician's attention. These relevant phenomena are called "symptoms".

Of course, there are different psychopathological paradigms (among which biomedical, psychodynamic, phenomenological, etc.), and each paradigm has its own hierarchy of priorities (which should be the clinician's focus of attention) as well as its own concept of symptom. As a consequence, the concept of symptom covers a vast array of indexicalities. In biological medicine, a symptom is the epiphenomenon of an underlying pathology. Red, itchy and watery eyes, congestion, runny nose and sneezing, sometimes accompanied by itchy ears and buzzing sound, itchy and sore throat, cough and post-nasal dripping are known to be the manifestation of an inflammation of the respiratory apparatus.

But long before we found out what was the cause of these disturbing phenomena (namely rhinovirus infection), we all knew that they were the symptoms of a mild, although distressing and untreatable, disorder called the "common cold". Within the biomedical paradigm, a symptom is first of all an index for diagnosis, i.e. it is used by clinicians to establish that the person who shows that symptom is sick (rather that healthy), and that he or she is affected by a particular illness or disease.

The principal utility of any system of medical taxonomy relies on "its capacity to identify specific entities to allow prediction of natural history and response to therapeutic intervention" [6]. The biomedical understanding of "symptom" is clearly coherent with this. Biomedical research aims to sharpen its tools to establish increasingly more reliable and valid diagnostic criteria. Its real ambition is not simply to establish a diagnosis through the assessment of clinical manifestations (i.e. symptoms), but to discover the causes of these symptoms (aetiology) and the pathway that leads from aetiology to symptoms (pathogenesis). "Ultimately, disease specification should be related to events related to causality rather than simply clinical phenotype" [6]. It is assumed that progress in medicine is dependent on defining pathological entities as disease based on aetiology and pathogenetic mechanism – rather than as clinical syndromes based on symptom recognition. In the biomedical paradigm, the truth about a symptom is its cause. The main, more or less explicit, assumptions in the biomedical paradigm are the following: 1) each symptom must have at least one cause, 2) this cause lies in some (endogenous or exogenous) noxa affecting the living organism, 3) the presence of a symptom causes some kind of dysfunction (cause → symptom → dysfunction). Also, 4) if we want to eliminate a symptom, we should eliminate its cause or interrupt the pathogenetic chain that connects its putative aetiology with the symptom itself. Thus, the biomedical paradigm is a knowledge device based on the concept of "causality". In general, causality (in the biomedical paradigm) goes from aetiology (in our example, the presence of a virus), to symptom(s) (breathing difficulties), to dysfunction (poor physical performance due to blood hypo-oxygenation, thus reduced adaptation of the person to his or her environment).

An important, implicit assumption is also that symptoms are considered accidental, i.e. non-essential to the living organism, whereas the absence of symptoms is considered essential – i.e. normal to living organisms. In other terms, health is considered normal, whereas disease is considered abnormal.

Many of these assumptions – if we apply this paradigm to the field of mental pathology – are at least controversial, or even counterfactual. What is of utmost interest here is the fact that in the biomedical paradigm, symptoms have causes, not meanings. Moreover, we can assume that a symptom is not an accident to that person; rather, it displays his true essence. As such, it is the contingent opportunity of a possible encounter between the person and alterity. Symptoms are the via regia to recognition as they express the person's vulnerability. Someone's vulnus displays what is most personal and intimate to him. "Come inside – says Eumeus to Ulysses when he arrives at his hut – and when you have had your fill of bread and wine, tell me where you come from, and all about your misfortunes" (Homer, Odyssey, 2005, XIV, p. 47). Only after Odysseus had a hearty meal of pork does Eumeus ask about his story: "And now, old man, tell me your own story; tell me also, for I want to know, who you are and where you come from. Tell me of your town and parents, what manner of ship you came in, how crew brought you to Ithaca, and from what country they professed to come – for you cannot have come by land".

The recognition of Ulysses in the episode of Euryclea – Ulysses' wet-nurse – comes with the recognition of his scar. As Euryclea is putting Ulysses' feet in a basin of water, she notices a scar on one of his feet. She immediately recognises it as the scar that he received when he went boar hunting with his grandfather Autolycus: "As soon as Euryclea had got the scarred limb in her hands and had well hold of it, she recognised it and dropped the foot at once. The leg fell into the bath, which rang out and was overturned, so that all the water was spilt on the ground; Euryclea's eyes between her joy and her grief filled with tears, and she could not speak, but she caught Ulysses by the beard and said, 'My dear child, I am sure you must be Ulysses himself, only I did not know you till I had actually touched and handled you'" (ibid., XIX, p. 392).

This myth has a clear correspondence in Karl Jaspers' concept of "cypher" [7]. "Cypher-reading is the primary requisite of manhood" [7]. Cypher-reading is an essential character of being a man. Cyphers show what without

them would remain implicit for us. Symptoms are a special category of cyphers: through them alterity, that is the hidden yet operative (and perplexing, or disturbing) dimension of our existence, is made manifest. Like a patient's symptom, which is not accidental to that patient but is rather the manifestation of his or her true identity, cyphers are the contingent opportunity of recognition, that is, of a possible encounter between the person and the encompassing dimension of her existence.
The cypher must keep on an inexhaustible signification with which no definite interpretation is commensurate [7]. If the cypher "becomes fixed and definite and turns into an object, then it loses its essential force. It collapses into a sign" [7]. Cyphers must not be crystallised into a kind of definite, categorical concept. The meaning(s) of the cypher must be kept "in suspension" – remain unsaturated [7]. The defection from the cypher to the pure concept (as occurs when the cypher grows a single meaning), as well as the interpretation of a cypher as if it were a symbol (such as when the cypher is interpreted through an 'other'), destroys the force of the cypher.

Symptoms in phenomenological psychopathology

Phenomenology is essentially concerned with laying bare the structure of the life-world inhabited by a person. A symptom is a feature of a person's life-world whose meaning will be enlightened by grasping the deep architecture of the life-world itself and the person's invisible transcendental structure that projects it. Life-world is the original domain, the obvious and unquestioned foundation of our everyday acting and thinking. In its concrete manifestations it exists as the "realm of immediate evidence". Although the majority of people are situated within a shared life-world, there are several other frameworks of experience – for example, fantasy worlds, dream worlds, and "psychopathological worlds" [8]. Abnormal mental phenomena are the expression of a modification of the ontological framework within which experience is generated. The overall change in the ontological framework of experience transpires through the single symptoms, but the specificity of the core is only graspable at a more comprehensive structural level [9]. The experience of time, space, body, self and others, and their modifications, are indexes of the patient's basic structures of subjectivity within which each single abnormal experience is situated.
Before we proceed in this direction, I need to clear the ground of a possible misunderstanding. To consider phenomenology as a purely descriptive science of the way the world appears to the experiencing subject is a serious mistake, although it is true that phenomenology sponsors a kind of seeing that relates to something already there, rather than to what stands before, beyond or behind what is existent. "Making the invisible visible" can instead be taken as the motto of phenomenology, just as it was the passion that possessed many of the artists of the twentieth century and the intellectual motor of the major scientists of the "invisible century," including Einstein and Freud, in their search for hidden universes.
The symptom is conceived as a part of a discourse, to be deployed and analysed as a text. The issue, then, is how to rescue its invisible and unintended meaning. All human deeds can be produced or reproduced as a text. The text – be it oral or written – is a work of discourse that is produced by an act of intentional exteriorisation. One of the main characteristics of a text is that once it is produced, it is no more a private affaire, but is of the public domain. It still belongs to the author, but it also stays there independent with respect to the intention of the author.
The externalisation of one's actions, experiences and beliefs via the production of a text implies their objectification; this objectification entails a distantiation from the person herself and an automatisation of the significance of the text from the intentions of the author. Once produced, the text becomes a matter for public interpretation. Now, the author's meanings and intentions do not exist simply for-himself, but also for-another.
This process of objectification and of automatisation is nicely described in Hegel's theory of action [10] that was explored in the previous section. Indeed, there is a parallel between a text and an action. Just as every action involves a recoil of unintended implications back upon the actor, every text – including symptoms – implies a recoil of unintended meanings back upon its author.
Whenever we act, via the externalisation of our intentions, we experience a kind of alienation and estrangement from ourselves. We discover alterity within ourselves. The symptom deployed as a text exposes its author to this very destiny. A text is the product of an action, a linguistic action. Like all actions, once produced the text shows the disparity between the author's conscious intentions and unintended consequences. The symptom exposed as a text recoils back upon its author, displaying the discrepancy between the private intended sense and its public tangible result. The text, as the tangible result of a linguistic act, with its unintended consequences, reflects – makes visible – the "mind" of the author much more faithfully than a simple act of self-reflection. To paraphrase Hegel, the "mind" cannot see itself until it produces a text objectifying itself in a social act. Because all conscious intentions are incomplete, self-reflection is just an incomplete form of self-knowledge. A person cannot discern alterity within himself until he has made of

himself an external reality by producing a text, and after reflecting upon it.
The production of a symptom is simply a particular case of this general rule. As a text, in the symptom alterity becomes manifest. A symptom is the outcome of an interrupted dialogue between the person and alterity. The symptom is nothing but a text by which an unrecognised alterity is made manifest. When alterity is no more integrated into the narrative, the person fabricates about oneself, and a symptom is produced as an extrema ratio for alterity to become discernible. The symptom is the last chance for the person to recognise themself.
This is a kind of understanding that "seeks to find the logos of the phenomena in themselves, not in underlying subpersonal mechanisms" [11]. The symptom, then, is an anomaly, but not an abnormal, aberrant or insane phenomenon in a strict sense. Rather, it is a salience, a knot in the texture of a person's life-world, like a tear in the matrix. It is a place that attracts someone's attention, catches one's eyes and awakens one's care for oneself in a double sense. The symptom reflects and reveals alterity in oneself – in it alterity becomes conspicuous. From the vantage offered by the symptom, one can see oneself from another, often radically different and new, perspective.

The case of gender dysphoria

An illustration of the vulnerable duplicity inherent in the human condition and of the emergence of symptoms as the cypher of a miscarried dialogue with alterity can be taken from gender dysphoria, where the person suffers from a marked incongruence between his or her experienced gender and the assigned sex, for instance, a person living with a man's body who struggles to shape his body as a female body. In gender dysphoria, the dialectics between one's sexual body as alterity and one's identity comes to a stop. The core symptom of this disorder is dysphoria, that is, an unpleasant mood state characterised by uneasiness, irritability, restlessness and despair.
The point I want to make becomes clearer if I reformulate the dialectic between the person and involuntary dispositions is that between form and matter. I am not merely the matter of which I am made. Rather, I am that matter plus the form that I impose upon it. Obviously, the matter of which I am made (into which I am thrown) – my Whatness – delimits the possibility for me to assume the form that I would like to impose upon it as an autonomous person – my Who-ness. In trying to shape my matter, I experience myself as an autonomous person and, simultaneously, as a person whose autonomy is limited by the matter itself.
Matter, in this case, is the body itself, the body into which I am thrown, its facticity, including its sex, as well as height, weight, colour, etc. My body is perhaps the most intimate part of the person that I am, but at the same time it can turn out to be the most extraneous. My material body is transcendental to me. At a certain moment in my life, I may realise that I have a material body that is clumsy, vulnerable and mortal, and that impedes my ability to be what I want to be. My body manifests itself as alterity. This paradigmatically happens through the experience of shame. Shame is an affect that awakens and focuses my attention. When I feel ashamed, I am aware of being seen by another person whose gaze uncovers a part of who I am, usually a part that makes me feel embarrassed, inadequate and humiliated. The effect of shame is that it reduces the complexity of the person that I am to one single aspect of it: when I feel ashamed I know that for the other I am nothing but that specific feature of the complexities of who I am. "With the appearance of the Other's look – writes Sartre [12] – I experience the revelation of my being-as-object". The upshot of this is a feeling of "having my being outside (…) [the feeling] of being an object". Thus, one's identity may become reified, and reduced to the external appearance, to the matter or Whatness of one's own body.
In a famous movie by Pedro Almodovar, All about my mother, the transvestite Agrado offers a monologue about her becoming who she chose to be as an alternative to what she was born to be. "Aside from being pleasant", she says, "I am also very authentic", and she lists the various types of surgical operations she has undergone to become so authentic. Agrado's identity is not simply determined by her originally masculine body, rather she shapes that body according to her experience of being the person that she is. She ironically says: "It costs a lot to be authentic" and continues, "All I have that is real are my feelings and these pints of silicone". Gender, according to Agrado, is not simply a physical fact, rather an accomplishment.
Gender to her has a moral value, since it is not confined to the physical manifestation of one's natural body, but entails a choice. In other terms, gender is a more complicated thing than what we consider to be more readily stipulated natural kinds, such as an apple, a pear, or a person's biological sex. Gender is a personal experience, heavily sensitive to socio-cultural norms and conventions, which makes it a vulnerable part of a person's autonomy. Between sex and gender there is the same relationship as between matter and form. We can shape the matter we are "thrown into" and give it the form we desire, obviously within the boundaries delimited by matter itself and by our capacity for autonomy. Being the person that I am is a task and a responsibility that consists in becoming who I am through what I am.

What is "dysphoria" in gender dysphoria?

Being a person, that is, achieving personal identity, for Agrado is a fragile dialogue between assigned sex and desired gender. The symptom of this discrepancy between sex and gender is dysphoria. Agrado would probably (and perhaps erroneously) be diagnosed as affected by gender dysphoria. Dysphoria is an emotional state saturated with a brimming constellation of feelings without any explicit object or target, a state of tension that may lead to spontaneously vigorous outbursts as well as to pale stagnation or emotional depletion. Dysphoria is empty intentionality devoid of the moderating power of language and representation that reflects the person's fragmented representations of oneself and of others and induces painful experiences of incoherence and inner emptiness, threatening feeling of uncertainty and inauthenticity in interpersonal relationships, and excruciating sense of the insignificance, futility and inanity of life. Persons affected by dysphoric mood experience their own self as dim and fuzzy, feeling deprived of a defined identity and unable to be steadily involved in a given life project or social role. Also, they may see others as cloudy, and their faces as expressionless. But it also entails a sense of vitality, although a disorganised, aimless, and explosive one – a desperate vitality. Dysphoric persons experience their mood as a disordered flux, an overwhelming power that is at the same time a disturbing, disorganising, and compelling source of vitality. Dysphoric mood is felt as creative and destructive at the same time: a vigour that brings life as well as annihilation. On one side, this power is a violent spasm that takes control of the body and destroys the organising embodied structure of the intentional engagement with the world. On the other side, it is also a power that expresses vitality in touch with the source of all sensations. It augments the sense of being alive through an unmediated feeling of life in all its dynamic potentiality, before being committed to the structure and representation that shape and orient what we consider to be a "normal" human life.

Dysphoria, that is, in the case of gender dysphoria, uneasiness and concern with one's body facticity, is the symptom of the fragility of the dialogue between the person and the obscure intimations that stem from one's body, especially in early phases of this disorder. The interruption of this dialogue might have caused Agrado to fall into being what she does not feel and want to be – a man – or vice versa to identify with what she is not and she cannot be – a woman. Agrado's identity is the unstable, yet mature, point of equilibrium between these two poles. Falling into her Whatness, that is, not recognising her uneasiness with being thrown into a male body and her desire to be a woman, will seemingly originate some sort of neurotic symptoms, for instance a kind of phobia (e.g. so-called social phobia), or more severe psychotic phenomena, such as a delusion of reference.

Her remaining unaware of her desire may originate a distressing kind of bad mood like dysphoria and its sequelae. Unless she recognises her desire to be a woman, she will be unable to decipher these disturbing experiences as expressions of the non-coincidence with herself, thus she will be unable to appropriately make sense and cope with them.

On the other extreme, the exalted fixation on being, or fully becoming, a woman – rather than the awareness that her desire will never become completely, but only partly, fulfilled – will also originate some sort of symptomatic phenomena. For instance, it may originate dysmorphophobia (body dysmorphic disorder) and (as the culture of late modernity promises that one can modify one's own material body at one's own will) an escalation of medical consultations and surgical interventions.

The fulfillment of Agrado's desire consists on her satisfaction for having decided to become a woman (gender), based on her recognition of her desire, and for striving to achieve a female form that reflects her desire, rather than on her being a woman (assigned sex). In other terms, Agrado's satisfaction is based on her mature awareness that she will never fully appropriate her identity as a woman, that for her it will remain a perennial task. In this sense, her satisfaction for her being-so with respect to her wished-for identity is by no means different from that of any other human being.

This is confirmed by the real case with Kate Bornstein, a transsexual (M to F) person who says about herself that she does "deceive herself about being a woman" [13]. To her, being a woman is a "performance", a continuous task, rather than a fact. This is the case with all gender identity – she holds – and for all identity in general. "The bipolar gender system" she writes, serves as a kind of safe harbor for most of us, and I'm definitely including myself in that, even though I don't personally identify as either a man or a woman, because I walk though this world appearing to be a woman for the most part. I pass as a woman. I can do that. And I do because it allows me to rest for a moment" [13]. This is nicely encapsulated in the following lines:

> I grew this body.
> It's a girl body. All of it.
> Over the past seven years every one of these cells
> became a girl, so it's mine now.
> It doesn't make me female.
> It doesn't make me a woman.
> (ibid., p. 233.)

In a similar vein, gender identity is considered "performative" by Ricky Wilkins [14]. These two seem to be cases of

well-carried (rather than miscarried) transsexual existence – and, in general, of mature dialogue with alterity.

Phenomenological psychopathology and care

The challenge facing the clinician is how to offer the patient an insight into their fragile personhood, that is, into the alterity one experiences in oneself – e.g., a dysphoric feeling about his/her "natural" sex – as well as helping one to understand how they try to make sense of this and, moreover, to acquire the appropriate means to cope with their unease. Hermeneutical phenomenology is a resource when dealing with this challenge of therapy because of three basic features of this philosophical approach to human personhood.

First, the phenomenological character of the approach provides a theoretical framework to assess and explore the patient's experience of troubled personhood. This is an important methodological contribution to therapy, since it is open to an unusual extent, in that it reveals aspects of experience that other approaches tend to overwrite or eclipse with their strong theoretical – and sometimes moralistic – claims. In this sense, we can say that the ethics of this approach is based on the principle of letting the patient have his or her say. This principle admonishes the clinician to bracket their own prejudices and let the features of a pathological condition emerge in their peculiar feel, meaning and value for the patient, thus making every effort to focus on the patient's suffering as experienced and narrated by them.

Second, the phenomenological articulation of the dialectics of selfhood and otherness gives the clinician an epistemic tool with which to understand how the struggle with one's involuntary dispositions makes personhood not just a fact, but also a problem. The vulnerable character of personhood that is so dramatically expressed in mental disorders is closely connected with the problem of the fragility of human identity, that is, with the problem of our cares and concerns. Making sense of what we care about and how we care about being the particular person we are involves the responsibility for one's being-so, that is, for one's vulnerable and troubled personhood. This responsibility implies how to respond to the challenges involved in discovering alterity in one's own self, how to make sense of one's troubled personhood and how to become the person that one is.

Third, the hermeneutical character of this approach provides a framework by which the clinician can make sense of norms and values involved in a person's struggle with their involuntary dispositions. We care about being persons, and the hermeneutical emphasis on both the What and Who of the person that we care about being and becoming – that is, both the a-rational, biological values and the rational, personal values at work in our care – provides the clinician with a framework with room for the ethical problems involved in being a person.

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The role of psychopathology in the new psychiatric era

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Summary

The recent increase in mental health problems probably reflects the fragmentation of social cohesion of modern society, with changes in family composition, work and living habits, peer communication and virtual-based reality. Fragmentation can also be due to the rapid expansion of urban agglomerations, too often chaotic and unregulated, the increase of market illicit substances, the reduction of social networks and the increase of social distance among people. As society changes, psychiatry has to adapt its role and target, moving from the treatment of mental disorders to the management of mental health problems. This adaptation will require a re-examination of the paradigms of psychiatry on which mental healthcare professionals have based their practice over the last century. Re-examination should include the paradigm of mental disorders as nosological entities with the development of a new psychiatric nosology, the concept of single disease entity, and a patient-centered psychopathology, since actual descriptions are not able to catch the inner world and reality of patients with mental health problems. Some of these changes will be highlighted and discussed in this paper.

Key words

Psychopathology • Biopsychosocial model • Nosology and classification of mental disorders • DSM-5

Introduction

Since the institution of asylums, which had been functioning for several centuries, introduction of antipsychotic drugs brought about a revolution. In many parts of the world by the middle of the 20th century, asylums had started to close and patients were being treated in the community. Towards the latter part of the same century, the focus shifted towards basing treatments at home and functional teams in many parts of the world. These changes reflect progress of psychiatry [1].

The role and target of psychiatrists in the last century changed from the custody of the insane to the treatment of mental disorders and to the management of "mental health problems", which are not proper mental illnesses, but rather the consequences of psychological stressors [2]. The question of defining mental illness remains an important one. In many settings, terms such as mental health issues, mental health problems and even mental health concerns have been used, which all under-estimate the seriousness of mental illness and its burden on society. There is no doubt that many of these "problems" may be due to the many social changes, economic upheavals including ongoing economic downturn, revolutionary advances of knowledge and to other developments. All this now requires a serious re-examination of the paradigms on which psychiatry and mental health care have been based in the last century [3-6].

The fragmentation of social cohesion, which has determined changes in family composition, working and living habits, problems in peer communication and the constitution of virtual-based realities, has brought many of these problems to the attention of mental health professionals. Other factors, which may have contributed to the rise of modern mental health problems, include the rapid expansion of urban agglomerations, too often chaotic and unregulated, the increase of online marketing of illicit substances among the youth [7], the reduction of social network and the increase of social distance among people [8].

Addressing these changes should be a priority for psychiatrists and psychiatry as a profession. The question is how these roles are redefined in this changing context [9]. The debate over the role of the psychiatrist has been going on for decades. This is the case for the "bio-psycho-social model", that from its identification in early '70s has been progressively transformed into a "biomedical model" with the consequences at times that the psychological and social factors involved in the aetiopatogenesis, management and treatment have been disregarded [10]. Another issue is the case of psychopathology, whose original definition as the "the study of the abnormal phenomena of mental health" [11], has been reduced to its descriptive nature and is no longer considered as the psychiatric science used to ac-

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cess to the patient's inner world [12 13]. In this paper, we explore the relationship between changing psychopathology and social systems.

The biopsychosocial model

Recently, Frances [14] published a provocative editorial on "Resuscitating biopsychosocial model". The title is evocative of someone or something that is disappearing and should return to live. The author questioned the current debate on the future of psychiatry and its current conceptual crisis. Is it the rediscovering of a previous model or a way to enter in a new fruitful period of the discipline? The limitations of current diagnostic criteria and the failure of neurobiological research are among the possible factors behind this "crisis" [15-17]. In this framework, psychiatry needs to adapt to a different social context; as society changes, psychiatrists have to adapt their target [18].

At the beginning of the 1970s, several major challenges threatened psychiatry's credibility: the unreliability of psychiatric diagnoses, the presence of mental health hospitals where patients were admitted without appropriate treatments and the heterogeneity of models and theories to explain the psychopathology of mental disorders. At that time, psychiatry was facing a crisis and the public image of psychiatry was temporarily restored with the publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), the beginning of the deinstitutionalisation process and the identification of the biopsychosocial model of mental illness [14]. Several authors have argued that the bio-psycho-social approach to mental illness has been progressively reduced to a mere biological model [14 19], with the discovery of the importance of neurotransmitters and of receptor systems in the aetiopatogenesis of mental disorders. However, despite encouraging progresses made in this field in the last years, this approach failed to identify the pathophysiological bases of mental disorders [20], as a neurobiological phenotypic markers (or genes) useful for diagnosis in psychiatry are still missing [21 22]. The most evident consequence of this failure is that progresses of neuroscience have not had an impact on psychiatric practice. The enthusiasm brought about by a period of exceptional progress of research in neuroscience has been followed by some disillusionment [23]. Another element which favoured the adoption of the biological model was the commercialisation of the first drugs for treatment of psychiatric disorders in the late 1950s. Since then, pharmaceutical companies strongly encouraged both research in the field of neuropsychopharmacology and in psychiatric practice. In fact, the "pill and appointment" became the dominant psychiatric treatment, and evidence on the effectiveness of antidepressants, mood-stabilisers and antipsychotics helped to the shift from the biopsychosocial model to "the bio-bio-bio model" [10].

Recent developments in mental health science have clearly demonstrated that causes or risk factors of mental disorders can operate at many levels, including genetic, neural, individual, family and social [24]. The recognition of the multifactorial aetiopatogenesis of mental disorders clearly shows that a reconsideration of the biopsychosocial model is needed. Depending on the specific situation, the biological level can be more or less relevant with respect to the social or to the individual psychological level [25]. This new approach has obvious diagnostic, clinical and therapeutical implications, which will be discussed in the next paragraphs.

The "operational revolution" and the rediscovery of psychopathology

The publication of the DSM-III signed the so-called "operational revolution", a radical remark in which the body of clinical knowledge and descriptions of mental disorders were shortened and simplified into labels and well defined psychiatric syndromes, available for the general public and deprived of their theoretical background [26]. Differently from DSM-III, the two previous editions of the manual did not adopt a categorical approach to mental disorders. In fact, the DSM-I, published in 1952, relied mainly on psychodynamic concepts of diagnosing psychopathology, dividing mental disorders into the standard psychoanalytic categories of neurotic, psychotic, and character disorders [27]. Moreover, in the first edition of the DSM the term "reaction" was extensively used throughout the manual, underlying that mental disorders derive from a "reaction" in response to emotional states brought on the circumstances of life [28]. The second edition of the DSM, published in 1968, continued to conceptualise psychopathology from a psychodynamic perspective, keeping the overall approach adopted by the first edition of the DSM. Despite this, several changes in terminology were made, in order to make it comparable with ICD-8 [29]. Only with the publication of DSM-III the operational criteria were formulated. The introduction of explicit diagnostic criteria, initially only for research purposes and subsequently also for use in regular clinical practice, had the main aim to overcome the subjectivity in the diagnostic process and was also a response to the foothold that psychoanalysis had on practice of psychiatry in the USA. Interestingly, the authors of DSM-III clearly stated that the use of operational criteria did not exclude clinical judgment, and that the use of fixed labels in psychiatric diagnoses requires a "considerable amount of clinical experience" and knowledge about the underly-

ing mechanisms of abnormal phenomena. Although operational criteria should have been used only as "suggested criteria" in order to standardise psychiatric diagnoses [30], structured diagnostic interviews and checklists progressively became the most frequently used instruments to make psychiatric diagnoses [26]. As a consequence, psychopathology has been neglected in recent generations of psychiatrists, in-depth descriptions of mental abnormal phenomena and syndromes [31] have simply been removed from psychiatric educational programmes, and the term "psychopathology" has been used in a trivial way, referring to the subject matter of psychiatry, instead of the discipline that studies the phenomena of mental disorders [32-33]. In fact, following the operationalisation revolution, psychopathology was emptied of its original meaning and became synonymous of symptomatology (the study of isolated symptoms) or nosology (the study of psychiatric diseases intended as a combination of symptoms) [34]. The dehumanisation of psychiatric clinical encounters and of the psychiatric profession as a whole has been one of the most evident consequences of this "operational revolution".

However, operational criteria also did something good for psychiatry, since they provided psychiatric diagnoses with good scientific evidence and helped to fight irrational and unscientific attitudes toward psychiatry [35]. In fact, before the publication of the DSM-III, psychiatric diagnoses were criticised for their lack of objectivity and the scarce reliability – the diagnostic agreement among two psychiatrists on the same evaluation was little more than random chance [30]. Since the DSM-III, loss of subjectivity and agreement among researchers or clinicians has led to better diagnoses. However, the role of insurance companies in pushing for inclusion of many diagnostic categories, which have not found an adequate counterpart in the clinical practice, needs to be acknowledged.

The need to rediscover psychopathology as the basic science of psychiatry has been claimed by several experts worldwide, and represents one of the educational priorities for early career psychiatrists [9]. A recent survey carried out in 32 European countries found that training in psychopathology during residency is not fully satisfying, and that the number of hours dedicated to training in psychopathology is limited and far from adequate [10]. These data show that, if psychiatry wants to enter a new era it needs to rediscover its basic sciences, such as psychopathology, in order to better understand the inner experience of its patients and provide patients with appropriate and integrated treatments.

Diagnoses 2.0: the DSM-5 era

The Diagnostic and Statistical Manual of Mental Disorders (DSM) provides the standard language by which clinicians, researchers and public health professionals communicate about mental disorders [36]. This has been used since its first publication in late 1950s, mainly in the United States, while other countries have adopted the *International Classifications of Disease* (ICD), developed by the WHO. The initial versions of both manuals had similar but separated criteria, and several efforts have been made to harmonise diagnostic labels and criteria between these two classification systems. The DSM-5 Task Force and the ICD-11 Development Advisory Committee have created a more valid basis for the organisation of a classification of mental disorders. At the current status, the groups of disorders ("blocks") proposed for the ICD-11 will be overlapping with those included in the DSM-5. The ICD-11 classification will remain based on descriptions of the prototypes of the various mental disorders rather than on operational diagnostic criteria as in the DSM-5 [37 38].

Many significant changes have been included in the DSM-5. Some disorders have been revised by combining criteria from multiple disorders into a single diagnosis [9], new disorders, such as the disruptive mood dysregulation disorder, the binge eating disorder and the dysphoric mood disorder, have been included, the number of specifiers and subtypes has been expanded or removed, and a section on "Conditions for further study", including the "Attenuated Psychosis Syndrome", the "Internet Gaming Disorder", the "Persistent Complex Bereavement Disorder", the "Suicidal Behavior Disorder" and many others, has been added [36]. However, even in the latest version of the DSM, psychiatric diagnoses continue to suffer from heterogeneity within disorders, blurred boundaries between disorders, frequent use of "not-specified" categories and high rates of comorbidity [39]. Despite many innovations, the publication of the DSM-5 raises several doubts and questions regarding the categorical approach [40]. The use of fixed labels and rigid inclusion criteria does not permit to consider the clinical heterogeneity of symptoms with the consequence that DSM-5 sensitivity in detecting a clinical condition is greatly diminished. Another major problem with the DSM-5 is that several diagnoses, such as those related to the use of new technologies and to the spread of new synthetic drugs, are still not present.

Therefore, modern classification systems are still not able to capture the inner world and reality of patients with mental health problems and are thus not entirely satisfactory. An integration of psychopathological descriptions, operational diagnostic criteria, social and environmental changes, individual factors and biological substrates is needed to have a clear picture of persons suffering from mental disorders. A single-view approach is probably misleading and will generate several diagnostic and ther-

apeutic difficulties in future generations of psychiatrists.
To overcome the limitations of current diagnostic classification systems, a new framework has been proposed by the National Institute of Mental Health, called Research Domain Criteria (RDoC) program, with the aim to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behaviour and neurobiological measures" [41]. The RDoC is proposed as an alternative to the ICD/DSM systems and includes the integration of neurosciences with behavioural sciences and a qualitative dimensional approach to psychopathology. The RDoC reflects a wider conceptual framework that considers mental disorders as the result of several individual ("e.g." the biological and psychological) and contextual ("e.g." social) factors. Of course, this programme has both advantages and limits. The RDoC represents a new framework for planning and carrying on research on psychopathology that can reflect advances in genetics and other areas of neurosciences and behavioural sciences [42]. One of the most important advantages is that this programme aims to incorporate a dimensional approach in psychiatric diagnoses. However, the RDoC programme has some potential disadvantages, since too little attention is given to the subjective experience and to patients' inner experiences [43], while attention is mainly on brain circuits. Moreover, the RDoC programme is used for research purposes, and is very far from being applicable in clinical practice [44] and therefore, there is still much work to do to make this programme useful for clinical practice [45].

Conclusions

There is no doubt that psychiatry is in a transition phase in which psychopathology, considered as a discourse (*logos*) about the sufferings (*pathos*) that affect the human mind (*psyche*), still plays a fundamental role. Of course, psychiatrists must be able to adapt their current practice to the new era, identifying protective and risk factors for mental illness, redefining their target, and founding their practice on integrating the biomedical approach with traditional psychopathological background.
In our opinion, to enter the new era, psychiatrists need to adopt an integrative approach to mental illnesses, taking into account that the clinical presentations of mental disorders are influenced by different and interplaying biological, psychological and social factors. In fact, on one hand there is no doubt that many psychiatric symptoms (such as delusions, hallucinations and anxiety symptoms) are the result of a dysfunction in brain circuits. On the other hand, evidence clearly shows the role of psychological (such as poor communication, temperamental and cognitive characteristics, poor self-esteem, low social competence and negative attributions) and social (such as social cohesion, social competencies, resourcing, housing, family context) factors in influencing onset, severity and outcome of mental disorders.
Nowadays, a modern psychiatrist cannot be anymore a neuroscientist, a physician, a psychotherapist or a social psychiatrist, but these different aspects of being a psychiatrist today should be integrated into one professional [46]. The different targets and approaches of psychiatry should be considered as a strength rather than a weakness of our discipline.

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Can the "connectomic way" provide a link between molecular neurobiology and phenomenological psychopathology? The case of schizophrenia

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Summary

Schizophrenia is a severe and complex mental illness whose aetiology remains unknown. Moreover, changing definitions of the diagnostic criteria of schizophrenia over past decades have not contributed to any substantial progress in terms of deeper pathophysiological understanding of the disease. Nevertheless, to date, significant evidence continues to be accumulated from epidemiologic, genetic and preclinical studies that point to a number of genetic factors that play important roles in the pathophysiology of schizophrenia, especially in terms of disrupted synaptic plasticity molecular processes. Specifically, the most recent approach in human research on schizophrenia is represented by "connectomics" or the study of connectomes, which can be defined as comprehensive maps of connections within an organism's nervous system. Indeed, it has been suggested that schizophrenic pathophysiology might rely on circuit-based dysfunctions that may represent the consequence, on a network scale, of the impairment in synaptic plasticity and neuronal connections that are increasingly found in preclinical molecular research, and that may stem from de novo and/or inherited disease-variants in target genes as well as from aberrant epigenetic mechanisms. On the other hand, circuit-based dysfunctions may underlie the defects in integration of higher-order cognitive functions that characteristically connote schizophrenia patients, and may account for aberrant self-experience which are typically described in phenomenological approaches to the disease. In this paper, we will critically explore the recent advances on molecular, genetic and neuro-imaging research in schizophrenia. Based on these data, we will emphasise the potential of the connectomic framework as an intermediate step between the biological and the phenomenological levels to capture the complexity of schizophrenia manifestations.

Key words

Basic symptoms • Subjective experience • Schizophrenia • Gene • FMRI • Transcriptome • Epigenetics

Introduction

Despite more than a century of extensive studies and descriptions, the clinical characterisation of schizophrenia remains elusive, almost like the borders of its spectrum conditions. As observed by Tandon et al. [1], "we know enough about the present construct of schizophrenia to recognize that it may be a conglomeration of disparate entities but our current knowledge is insufficient to delineate them". Indeed, from the original Kraepelinian construct to contemporary DSM-5 formulations, changing definitions of the diagnostic criteria of schizophrenia have not provided any substantial progress – at least in terms of deeper aetiological understanding.

Schizophrenia is syndromically characterised by several, often concomitant symptomatic dimensions, which are typically clustered in major dimensional sets (e.g. positive, negative, cognitive, disorganisation, mood and motor symptom dimensions). These abnormalities are differentially expressed throughout the course of the illness and encompass characteristic distortions of thinking and perception, interpersonal relating, communicational and cognitive impairments, affective flattening and restricted emotional resonance, motor abnormalities, avolition and apathy.

Beyond these descriptive domains, contemporary phenomenologically-inspired psychopathology has enucleated another cluster of phenomena, i.e. disturbances of the basic sense of self, as a core phenotypic marker of schizophrenia spectrum disorders [2 3]. This approach [4], which emphasises the psychopathogenic primacy of subtle disorders of self-awareness in the longitudinal development of schizophrenia spectrum conditions, offers an integrative and dynamic view of schizophrenia that coheres with recent trends in neuroscience. Briefly,

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despite the manifold, heterogeneous and varying presentations of schizophrenia, what seems to lie at the *generative* core of the disorder is an alteration of the basic framework of subjectivity, i.e. what allows us to "live our conscious life in the first person perspective, as a self-present, single, temporally persistent, embodied, and bounded (demarcated) entity, who is the subject of his experiences" [2]. In this sense, contemporary psychopathological research seems once again to return to a holistic, comprehensive view of schizophrenia that converges with the "connectomic" model emerging from genetics and neuroscience. The purpose of this paper is to offer an overview of the background coherence that links these multiple descriptive levels.

Genetics of schizophrenia

Evidence of a genetic contribution to the aetiology of schizophrenia dates back to early studies in twins and adopted offspring. However, in recent years, research on the genetic underpinnings of the disease has faced a profound acceleration due to the combination of large samples of subjects and technological advances. This has allowed the identification of a large set of "risk variants" that are defined as genetic elements that have been associated with an increased risk (i.e. susceptibility) to develop the illness. These risk variants occur across the entire allelic frequency spectrum, and are in many cases also associated with susceptibility for other neuropsychiatric diseases [5]. Moreover, several different types of genetic elements have been found in association with the risk of schizophrenia. Overall, risk alleles may be grouped in: 1) common alleles, which include single nucleotide polymorphisms (SNPs); 2) rare alleles, which include rare copy number variations (CNVs), single nucleotide variants (SNVs), and insertion/deletion mutations (Ins/Del); 3) *de novo* mutations, which include CNVs, SNVs or Ins/Del that arise from new (*de novo*) mutations on the DNA sequence.

A large number of common schizophrenia risk alleles have been identified by means of genome-wide association studies (GWAS). GWAS are large, often consortium-based studies where genetic associations are interrogated on a genome-wide basis in very large samples of schizophrenia patients. Through this strategy, it is now possible to detect the association that schizophrenia has with very common alleles that – given their low effect size – would not reach statistical significance in small or even intermediate size samples if considered independently. Indeed, each of these alleles has a weak effect on schizophrenia risk, with a mean odds ratio (OR) <1.2 (i.e. each allele increases the risk of schizophrenia by 1.2 times in subjects carrying the allele compared to non-carrying subjects). However, taken together, these risk alleles are thought to account for approximately 33-50% of genetic liability to develop the disease [6 7]. GWAS have clarified that schizophrenia may be conceptualised as a disease with a strong polygenic component involving thousands of common alleles [8 9], whose coexistence in the subjects causes a cumulative lifetime risk to develop the disease.

Apart from the earliest GWAS, only a few common risk alleles have been found to be associated with schizophrenia [8 10]; a recent study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) has identified 128 genome-wide significant associations in 108 discrete loci [11]. In this study, genome-wide genotype data were meta-analysed from 49 ancestry-matched, non-overlapping case-control samples including 34,241 cases and 45,604 controls, and from 3 European family-based samples including 1235 parent affected-offspring trios [11]. Among the 108 genetic loci identified, 83 have not been previously implicated in schizophrenia. Despite the fact that 75% of these loci contain protein-coding genes and an additional 8% were within 20 kb from a gene, only in 10 instances was the associated SNP credibly attributable to a known non-synonymous exonic polymorphism [11], i.e. determining a variation in the protein sequence of the gene's protein product. The vast majority of polymorphisms appear to exert their effects through the modulation of gene expression, by means of various genetic elements that will be discussed in the next sections. This assumption was partially corroborated by a confirmatory analysis showing that multiple of the credibly causal SNPs identified in the PGC study contained expression quantitative trait loci (eQTL) [11], which are genetic loci that explain a fraction of the genetic variance of a gene expression phenotype [12]. Notably, the PGC study also robustly confirmed the assumption that the polygenic risk score (PRS) can predict case-control status in independent samples [7 13]. PRS was generated on the basis of the observation that a considerable proportion of phenotypic variation in polygenic diseases can be explained by the ensemble of markers not achieving significance in independent GWAS studies [14]. Therefore, in previous studies, PRS had been constructed from alleles with modest-to-low statistical association with schizophrenia in GWAS studies [7 13] explaining, however, only a minor part of the liability variance. In the PGC study, PRS explained about 7% of liability variance [11], suggesting that this needs to be explored more thoroughly. Intriguingly, when individuals in three independent samples from those constituting the PGC mega-analysis were grouped into PRS deciles (i.e. with increasing number of common risk alleles with high-to-moderate statistical association with schizophrenia), the estimated OR of being affected consistently increased in each independent sample with

a greater number of schizophrenia risk alleles [11]. These results suggest that extensive efforts should be devoted to characterising the highest possible number of common risk alleles ranging from high to moderate association with schizophrenia, and to study their interaction on the genetic, and possibly, molecular level. Interestingly, among the loci significantly associated with schizophrenia were the DRD2 gene, a number of genes (as GRM3) involved in glutamatergic transmission and synaptic plasticity, voltage-gated calcium channels and genes implicated in immune response [11].

Epigenetics and transcriptomics of schizophrenia

Despite the strongest efforts to decrypt the genetic basis of schizophrenia, the great technological advances in molecular genetics suggest that the majority of genetic liability to the disease is generated by variations in post-transcriptional regulatory elements (epigenome) that control the expression of genomic sequences. Despite the fact that all gene expression regulatory events are often included among epigenetics, we will herein separately consider post-translational modifications of DNA and chromatin, often referred to as epigenetics in the strict sense, and RNA-mediated regulatory mechanisms.

Epigenetic mechanisms consist of DNA methylation and modifications of histone and/or chromatin structure. DNA methylation occurs via the DNA methyltransferase (DNMTs) enzyme, which contributes to transfer methyl groups to cytosine residues within CpG islands located in the proximity of gene promoter regions [15]. This enzymatic step transforms cytosine in 5-methylcytosine (5-mC), which represses gene transcription [16]. 5-mC may be further transformed into 5-hydroxymethylcytosine (5-hmC) by TET enzymes, which result in DNA demethylation and de-repression of gene transcription [17]. In schizophrenia, an over-representation of hypermethylated promoter regions has been found [18], determining a downregulation of several schizophrenia-related genes. BDNF, reelin (RELN) and COMT are among genes whose expression has been reported to be downregulated as a consequence of hypermethylation [19 20]. On the other hand, recent studies have demonstrated that TET1 and 5-hmC DNA modifications are increased in the cortex of schizophrenia patients [21]. Overall, it appears that the methylation state in schizophrenia patients may be altered, either in the sense of a hyper- or a hypomethylation on target genes. Notably, the methylation state by epigenetic mechanisms is also strongly affected by pre- and post-natal environmental factors, implicating that the level of gene expression is a dynamic phenomenon, with multiple regulatory steps that are variably modulated. For instance, reduced maternal care may alter both genome-wide and target gene methylation, and thereby their levels of expression, leading to enduring changes that modify adult behaviour and neurobiology [22].

The regulation of DNA expression is also mediated by non-coding parts of the genome. It has been estimated that, although at least 80% of the genome is actually transcribed, only a minor part (less than 2%) is constituted of protein-coding genes, with the remaining part is composed of non-protein coding elements [23]. Altogether these elements constitute the so-called transcriptome, which is the object of the most advanced research. Non-coding RNA has evolved with organism complexity, leading to an extremely sophisticated regulatory system in humans, which has been considered to have allowed the emergence of cellular complexity and higher-order cognitive processes, and is considered to underlie the tremendous complexity of the primate brain [24]. The most important non-coding RNAs belong to two major families: small RNAs (sRNA; less than 200 bp) and long non-coding RNAs (lncRNA; >200 bp). The former include: 1) small nucleolar RNA (snoRNA); 2) small interfering RNA (siRNA); 3) piwi-interacting RNA (piRNA); 4) microRNAs (miRNA), which are the most recent genomic elements to evolve, and repress gene expression by binding to transcribed RNA sequences with imperfect complementarity [25]. This strongly increases the range of target sequences that can be regulated by miRNAs, whose primary function is to interfere with protein expression and to promote transcript degradation. MiRNAs have been implicated in fine-tuning of neuronal plasticity [26] and have been considered to contribute to a supposed disruption of PSD-mediated synaptic plasticity in schizophrenia [27]. Reduction of miRNA expression, as in the case of the Dicer mutant (i.e. a transgenic mouse line lacking Dicer, the enzyme responsible for the maturation of piRNA and miRNA), is associated with enhanced learning and memory [28]. Indeed, reduced miRNA expression allows the translation at dendritic spines of mRNA encoding synaptic proteins that regulate synaptic functions [29]. On the other hand, however, a group of miRNAs, including miR-132 and miR-134, has been found to be increased by synaptic activity and may concur in enhancing synaptic strength, by promoting the expression of CREB or BDNF, which ultimately leads to dendritic spine formation and maturation [30]. These observations suggest that the type and direction of regulatory steps provided by sRNAs are extremely complex, and represent a tool by which evolution has obtained a remarkable scaling of human genome complexity.

Transcriptome analysis has recently gained interest as a technique to evaluate the whole part of the genome that is transcribed in schizophrenia patients. Distinctive

transcriptome alterations of PFC pyramidal neurons have been found in schizophrenia patients compared to both schizoaffective patients and non-affected controls [31]. Recently, transcriptome analysis of the human genome has reached incredible power, approaching the single base resolution by means of next-generation RNA-sequencing, thereby providing an extensive depiction of the developmental regulation of human cortex transcription across the life span [32]. This methodological approach promises to uncover the genome elements that could be differentially regulated in schizophrenia, and that could pre-date its neurodevelopmental course [33].

Molecular biology and molecular imaging studies

Molecular biology studies offer the opportunity to understand the molecular underpinnings of putative dysfunctions in schizophrenia and to relate them to distinct behavioural phenotypes relevant to the disease. In general, molecular studies (also often referred to as preclinical studies) are carried out in two systems: *in vitro*, i.e. in cultured cells, and *in vivo*, i.e. in animal models of the disease. Despite the great informative power of these studies, inference on the pathophysiological basis of schizophrenia, as well as for other psychiatric diseases, should be made cautiously given the intrinsic reductionism of transposing molecular alterations and behavioural phenotypes from animals to human beings. Notwithstanding these limitations, preclinical studies are essential to investigate putative pathophysiological models and to advance knowledge on the neurobiological functions of candidate genes or genomic elements.

An animal model of a disease should provide face, predictive, and construct validity. In schizophrenia, no animal model exists that can ensure complete validity in each of these domains, while the majority offer optimal validity in one or two domains, but not in the other(s), and researchers are used to choosing the animal model on the basis of their experimental aims.

Animal models offer different paradigms to study the molecular underpinnings of schizophrenia. Transgenic mice are experimental animals engineered to express rare mutations with variable penetrance, as when studying the neurobiological effects of these genetic variants (which may lie both in protein-coding or non-coding genome) and their behavioral correlates.

A myriad of transgenic mice models have been developed to study different molecular lesions that have been suggested to be present in schizophrenia, and many imply genetic alterations that directly or indirectly impair the neurobiology of glutamatergic neurotransmission and PSD-mediated synaptic plasticity [34]. Transgenic mice lacking the excitatory synaptic signaling scaffold IRSp53 showed impaired social communication and increased NMDA receptor activity in the hippocampus [35]. De novo mutations in the Shank3 gene found in a family with mental retardation and schizophrenia were expressed in a mouse line and showed aberrant glutamatergic synaptic plasticity [36]. Ddo(-/-) transgenic mice are an animal model of increased D-aspartate, which appears to have a protective effect against phencyclidine-mediated NMDA receptor hypofunction [37 38]. However, this animal model shows aberrant cortical-hippocampal connectivity at resting state MRI [37], thereby suggesting that sustained abnormally elevated D-aspartate levels and NMDA activation may play a role in the neurodevelopmental origin of schizophrenia. Altered hippocampal-PFC connectivity was also found in transgenic mice expressing a truncated isoform of DISC1 [39]. Remarkably, aberrant connectivity was associated with glutamatergic dysfunction, including attenuated cerebral metabolic response to ketamine and decreased hippocampal expression of NMDA receptor subunits 2A and 2B [39].

Another intriguing preclinical approach is the technique of gene expression molecular imaging that in some sense may combine, on the preclinical level, transcriptome analysis and functional neuroimaging. The technique allows a precise topographical description of the regions where specific genes of interest are expressed either in basal conditions or after a range of neurochemical, genetic, or behavioural manipulations, thereby providing a brain map of transcriptionally active areas. These studies have investigated expression levels of candidate genes for schizophrenia, whose neurobiological action is pivotal for PSD-mediated synaptic plasticity, such as Homer1a or GSK-3. Expression rates of Homer1a have been found to be modulated by different antipsychotics along distinct and antipsychotic-selective temporal and topographical patterns [40-43]. Moreover, expression maps of this gene are profoundly affected in animal models of the disease, such as after ketamine administration [44] or in phencyclidine-treated ddo(-/-) mutant mice [38]. Molecular imaging of gene expression has also been used to provide maps of functional connectivity changes among brain regions in distinct animal paradigms, such as chronic haloperidol administration [45], representing a preclinical correlate, with a high translational potential, of connectomics in humans.

Structural and functional neuroimaging

Research on schizophrenia determinants in the living patient has dramatically improved up to the evolution of fine neuroimaging techniques, such as computer tomography (CT) and magnetic resonance imaging (MRI).

These techniques were first, and are still, used to investigate structural abnormalities in brains of schizophrenia patients at different stages of disease, even in the prodromal stage, or in at-high-risk individuals, and in different ages. This approach had the merit of bringing attention to the disease-relevant brain areas and to progression of the disease along clinical stages.

Structural studies have allowed demonstration of a global reduction of brain volume in schizophrenia patients [46]. A recent systematic meta-review of structural brain alterations in schizophrenia revealed evidence of abnormalities in several brain regions [47]. The most replicated findings involved grey matter reductions of the anterior cingulate cortex, medial and inferior PFC, temporal lobe, hippocampus, amygdala, thalamus and insula [47 48]. Other brain regions have also shown alterations; however, these alterations were more likely due to disease progression or medication effects [47]. A recent advance in structural neuroimaging has been the advent of diffusor tensor imaging (DTI), which traces white matter tracts. The combination of MRI and DTI has been crucial to pool together data on structural abnormalities of grey matter and the anatomical connections among abnormal areas in schizophrenia patients, paving the way to the subsequent "connectomic" step of neuroimaging [49]. Indeed, a recent meta-analysis of DTI findings in schizophrenia has identified two white matter tracts with significant reductions: one connecting the PFC, anterior cingulate cortex and thalamus; and another one connecting the PFC, hippocampus/amygdala and insula [50]. Although it may be that disturbed connections in schizophrenia are not limited to the above-mentioned tracts, these studies have the great value of promoting a shift from a classical structural view to a more complex one, where relevance is given to how brain regions interconnect with each other, which may represent, on a neuronal circuit level, the mirroring of molecular alterations in synaptic plasticity and connections between neurons.

Structural neuroimaging, however, has the important limitation of being static, and thus does not provide a link between aberrant brain functioning and psychotic symptoms. This gap has been partially overcome by the advent of functional MRI (fMRI), which measures activity in target brain areas while the patient is actively carrying out specific behavioural tasks. One of the earliest and most reliable findings from fMRI studies has been the observation of PFC hypofunction during different executive functions, mostly working memory [51], although a more recent conceptualisation of experimental data points to an inefficient engagement of the PFC during executive functions in schizophrenia patients [52]. Intriguingly, decreased activation of the dorsolateral PFC during cognitive and emotive processing is one of the most significant findings in a meta-analysis of fMRI studies in at-risk individuals, and has been recently replicated in another sample of at-risk subjects [53 54].

A series of elegant studies has linked the expression of discrete allelic variants in candidate schizophrenia genes to brain activity during behavioural tasks, a research field known as *imaging genomics*. Indeed, in healthy individuals, greater PFC activity during working memory processes has been associated with functional SNPs that reduce the expression of dopamine D2 and serotonin 2A receptors (D2R and 5-HT2AR, respectively) [55]. The COMT genotype predicted differential parahippocampal and hippocampal activity during memory encoding in schizophrenia patients compared to controls [56]. In schizophrenia patients, the rs6314 non-synonymous variant of the 5-HT2AR gene was significantly associated with inefficient activation of the PFC during a working memory task, impaired working memory and attentional control, and poor response to olanzapine [57]. Although functional alterations in schizophrenia have been found in several other brain regions associated with aberrant behavioural tasks, the emerging concept is that functional abnormalities may derive from aberrant neural circuitry connection, a research field named *connectomics*.

Connectomics and psychopathology of schizophrenia

The connectome can be defined as the complete map of the brain's neural elements and their structural interactions that allow the complex integration and segregation of relevant information [58]. Connectomics has taken advantage of the development of resting state MRI (rsMRI), which explores the extent of connections between brain areas at rest. Indeed, decreased connectivity between the PFC and the thalamus under resting conditions have been described by rsMRI [59], which supports prior evidence of a direct correlation between reduced activation in the left dorsolateral PFC, rostral/dorsal anterior cingulate cortex and left thalamus during cognitive tasks [60].

Connectomics, which represents the most recent advance in human research on schizophrenia, is revealing all its promising potential, as it is putting a spin on the conceptual pathophysiological framework of schizophrenia. Indeed, schizophrenia is increasingly considered as a network-based disease, where dysfunctions in multiple candidate circuit networks concur to generate the complex and heterogeneous clinical phenotype [61]. Although a comprehensive connectome of the human brain remains a far distant scientific goal, one of the key advantages of such an approach lies in its revitalisation of the hierarchical system approach. Complex systems and network science are the methodological vectors that allow the

convergence of contemporary technological advances in neuroscience, capturing network connectivity across multiple spatial scales and accounting for individual variability and structural plasticity. One of the challenges of such approach is, however, to clarify how alterations of the connectome, while shaping brain dynamics, also support the multiple phenotypic manifestations of schizophrenia.

Traditional operational psychopathology of schizophrenia emphasizes the prominence of major symptom clusters: positive symptoms (e.g. delusions and hallucinations), negative symptoms (e.g. abulia, emotional-expressive flattening, passive/apathetic social withdrawal and an overall "disorder of relating"), and disorganisation (e.g. formal thought disorder, conceptual disorganisation, poor attention). Contextual to this triad, mania, depression, excitement, catatonia and lack of insight are usually considered as complementary to the dimensional structure of schizophrenia symptoms [62 63]. However, over and above canonical symptom domains, decades of empirical, phenomenological research in schizophrenia has revealed the topicality of anomalous subjective experiences. These are subtle, not-yet psychotic experiential distortions, which can be supra-organised and thematised into overt symptoms (such as positive, negative and disorganised ones) [2-4 64-67]. Anomalous subjective experiences incorporate two major, partly overlapping constructs: basic symptoms (BS) and self-disorder. The concept of BS was proposed by Gerd Huber [64] to indicate the early, immediate experiential manifestations stemming from the putative neurobiological substrate of schizophrenia vulnerability. BS were extensively catalogued in the *Bonn Scale for the Assessment of Basic Symptoms* (BSABS), and the concept of BS proved particularly important for early diagnosis, therapy, prevention and rehabilitation. Indeed, patients experience and communicate the BS as deficiencies with complaint quality and are able to cope with, adapt and compensate for them as long as the cognitive-affective complexity of the experiential field does not give rise to the emergence of productive-psychotic symptoms. Recently, a set of at-risk BS, denoting pre-psychotic prodromal states, has been operationalised in the context of new assessment tools derived from the BSABS (i.e. *Schizophrenia Proneness Instrument – adult and child/youth version* – SPIA/CY) [65 68 69]. The two at-risk criteria, i.e. the at-risk criterion *Cognitive-Perceptive Basic Symptoms* (COPER) and the high-risk criterion *Cognitive Disturbances* (COGDIS), indeed, identify help-seeking subjects early on and before the threshold of transition into productive-psychotic symptoms [69 70].

Strictly related to BS, Parnas and Sass' Self-Disorder (SD) notion specifically focuses on certain anomalous subjective experiences indicative of a pervasive perturbation of the very sense of being a self, endowed with a unique, stable and embodied first person perspective. Indeed, according to Sass and Parnas [4], schizophrenia involves subtle, enduring changes of "the experiential sense of being a vital and self-coinciding subject of experience or first person perspective on the world" [4]. SD includes an array of fleeting, yet irreducible feelings of estrangement and perplexity, distortions of the stream of consciousness and fluidity of the basic sense of identity, as well as transformations in bodily experience [71]. A detailed anthology of SD is presented in the *Examination of Anomalous Self-Experience* (EASE), a newly developed instrument that was specifically designed to support the psychopathological exploration of SD.

Although neither BS nor SD are incorporated in the current diagnostic criteria, they recur in the narratives of subjects vulnerable to schizophrenia, and have been captured by phenomenological psychopathology with expressions such as "loss of the natural evidence" (Blankenburg), "loss of the vital contact with reality" (Minkowski) or "inconsistency of natural experience" (Binswanger). Overall, the empirical literature on BS and SD reveals anomalous subjective experiences that:

- aggregate selectively among schizophrenia patients compared to other mental illnesses [66 72-75] and, among psychosis, discriminate schizophrenia from affective psychosis or other psychotic disorders [73 74];
- predict subsequent development of schizophrenia spectrum disorders [70 76 77];
- index pre-psychotic clinical high-risk populations [64 65 70], as well as genetically high risk ones [78 79];
- follow a gradient distribution in unaffected first degree relatives [80] and correlate with their subclinical schizotypal traits [81].

Overall, stratified empirical research shows that anomalous subjective experiences (BS and SD) delineate important phenotypes of the schizophrenia spectrum disorders, extending the potential for vulnerability characterisation to the "silent" (i.e. subclinical) side of the spectrum (including putatively schizotaxic individuals) [78 82 83].

Conclusions

Although a connection between the more recent advances in schizophrenia neurobiology and psychopathology appears hazardous, nonetheless, a speculative theoretical framework may be warranted. Circuit-based dysfunctions may represent the consequence, on a network scale, of the impairment in synaptic plasticity and neuronal connections that are increasingly found in preclinical molecular research, and may stem from *de novo* and/or inherited disease-variants in target genes as well as from aberrant

epigenetic mechanisms. On the other hand, circuit-based dysfunctions may underlie the defects in the integration of higher-order cognitive functions that characteristically connote schizophrenia patients, and that may account for aberrant self-experience, which are typically described in phenomenological approaches to the disease.

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Mixed states: still a modern psychopathological syndrome?

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Summary

Objectives

The aim of this review is to evaluate whether the DSM-5 concept of mixed features "specifier" provides a definition that reflects the richness and multiplicity of this psychopathological picture pointing out the historical development, clinical conceptualisation and proposed therapeutic approach to mixed states.

Methods

We review and discuss the recent evidence on the presence of mixed features during mania and depression and summarise findings on the conceptualisation of mixed states. Electronic searches of all English-language papers were performed in the MEDLINE and PUBMED database using and cross-listing key words: mixed state, mixed features, bipolar disorder, major depressive disorder, mania, hypomania, depression.

Results

The mixed categorical-dimensional concept used in the DSM-5 broadens the concept of mixed episodes, introducing substantial changes to the diagnosis of mixed states. This definition appears more appropriate for less severe forms of mixed states presenting clear and detectable mood symptoms with evident improvement compared to the DSM-IV, as the possibility of classifying depression "with mixed features".

Conclusion

The transition from the classical definition of mixed states to the one reported in the DSM-5 has determined a complex modification of the concept of mixed state. The DSM-IV-TR description, based on the co-presence of symptoms of opposite polarity, was extremely reductive and did not capture the sub-syndromal symptoms of the opposite pole experienced in bipolar and major depressive disorders. The DSM-5 definition of mixed features "specifier" represents a valid tool to improve the recognition and proper treatment of bipolar mixed patients, reducing misdiagnosis and mistreatment associated with chronic and repetitive exposure to antidepressants and sedatives, although the mixed categorical-dimensional concept does not adequately reflect some overlapping mood criteria, such as mood lability, irritability and psychomotor agitation.

Key words

Mixed state • Mixed features • Bipolar disorder • Major depressive disorder • Mania • Hypomania • Depression

Introduction

Mixed affective states are largely considered the simultaneous occurrence of manic and depressive features with a complex clinical presentation that frequently represents a real challenge for clinicians due to the evident difficulties in diagnosis, classification and treatment. The concept of mixed states introduced by Kraepelin was characterised by the presence of depressive and manic/hypomanic phases in manic-depressive patients and by the presence of a continuum between depressive and manic features. Though several authors had previously described the characteristics of mixed states, Kraepelin firstly provided a conceptualisation within a broader context, defining mixed states as the 'third polarity' of manic-depressive disorder and used this idea to consolidate his unified vision of this disorder. Through the years the concept of mixed states has been consolidated and the relevance of mixed states has been recognised, but the concept of a continuum between different affective states was excluded from the main psychiatric diagnostic systems (DSM and ICD). The failure of the DSM-IV-TR and ICD-10 in recognising mixed states together with the result of several studies on the topic encouraged many clinicians and researchers to reconsider the criteria for mixed episodes. In the DSM-5, the mixed episode as defined in DSM-IV-TR has been removed and sub-threshold non-overlapping symptoms of opposite polarity are identified using a mixed feature specifier to be applied to depression, mania and hypomania.

The history of the concept of mixed states

The first descriptions of a clinical condition that we currently would consider a mixed state appeared in the nine-

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teenth century (Table I); however, traces of what is considered to be a "mixed state" are present in antique medical textbooks (especially Aretaeus of Cappadocia) and in some treatises on psychopathology in the 1700s [1]. Heinroth, in his treatise entitled *Disturbances of Mental Life or Mental Disturbances* [2], was one of the first psychiatrists to explore mixed states in detail; he used a German term (*Mischungen*) translatable as "mix or mixture" to define psychopathological conditions in which discordant elements coexisted. Another German psychiatrist, Griesinger [3], described states of mental alteration in which melancholic and manic elements coexisted (as in Heinroth's descriptions), as well as forms that would be currently defined as rapidly cycling affective disorders. He defined such psychopathological conditions as "mid-forms" (*Mittelformen*), "in which a change from depression to the manic exaltation occurs", and described "Melancholia with destructive impulses" and "Melancholia with long-lasting exaltations of volition". In his view, then, mixed states could be often transitional forms.

In addition to the above authors, other European psychiatrists before Kraepelin described psychopathological conditions that had similarities to mixed states. For example, Jules Falret in 1861 described what he termed *État Mixte*, a condition characterized by "predominant ideas, often of sad nature, in the middle of an excitation state, simulating true mania". However, none of the cited authors provided a precise categorisation of psychopathological conditions in the manic-depressive area, including mixed states, which first appeared with the works of Wilhelm Weygandt and Emil Kraepelin. These two authors first conferred nosographic autonomy to mixed states in the context of Manic-Depressive Insanity.

Emil Kraepelin first used the term "mixed states" (*Mischzustände*) (Table II) starting from the 5th edition of his Textbook of Psychiatry [4], and maintained this term in the revised editions of the text [5 6]. He recognised as a significant contribution to his categorisation the work of his apprentice Wilhelm Weygandt, author of a pioneering monograph on the subject, the first book in the psychiatric literature on mixed states. Weygandt first described three conditions under the term *Mischzustände* (Table I), and recognised that these mixed states had a favourable outcome compared to schizophrenia (*Dementia Praecox*) ("when we deal with manic stupor, agitated depression, and unproductive mania, we can foresee a highly favourable outcome") [7]. Kraepelin, however, first provided a conceptualisation of mixed states within a broader context: he viewed mixed states as a 'third polarity' of manic-depressive disorder, and used this idea to consolidate his unified vision of this disorder (*The inner relationship of the apparently opposing conditions becomes most clear through the experience that there are fits of circular insanity in which excitement and depression are mixing in an inextricable way*) [6]. The possible co-occurrence of symptoms in the manic and depressive phases, seemingly antithetical, in his view confirmed the common association of two polarities of the same underlying disease, supporting a hypothesis that had been around since ancient times. Kraepelin identified a total of six different basic types of mixed states, depending on the combination of alterations in the three different psychic domains that, in his and Weygandt opinion, were involved in manic-depressive illness. The three domains consisted of mood (emotion), ideation (intellect, or thought) and motor activity (volition or *psychomobility* in Weygandt terminology). Each domain can fluctuate

TABLE I.
The development of the concept of mixed states (before Kraepelin).

Author	Definition
Heinroth, 1818	MISCHUNGEN (mixtures) – hypo/asthenias
Griesinger, 1845	MITTELFORMEN (middle forms) "in which a change from depression to the manic exaltation occurs": • melancholia with destructive drives • melancholia with long-lasting exaltation of volition
Falret, 1861	ÉTAT MIXTE (mixed state) "predominant ideas, often of sad nature, in the middle of an excitation state, simulating true mania"
Weygandt, 1899	MISCHZUSTÄNDE (mixed states): • manic stupor (elevated mood with psychomotor inhibition and decreased ideation) • agitated depression (depression with flight of ideas and agitation) • unproductive mania (elated mood with increased motor activity and inhibition of thinking) "When we deal with manic stupor, agitated depression, and unproductive mania, we can foresee a highly favourable outcome"

TABLE II.
Kraepelinian view of mixed states.

Kraepelin, 1893-1913	
Tripartite model: 1. affect 2. psychomotor activity 3. associative processes	MISCHZUSTÄNDE (mixed states) or MISCHLFORMEN (mixed forms): 6 types
Two general classes of mixed states	*1. Transitional forms*: a stage 2. in between, when depression changes to mania and vice versa
	3. Autonomous forms: mixed disorder on its own

around baseline in two directions: overall increase and decrease, giving rise to 2 states characterised by all 3 domains being in the same phase (classic mania and depression), and 6 mixed states, uniquely defined by asynchronous phase shifting of the 3 domains. Thus, he described the different mixed states of a) "manic depression or anxiety" (depressed mood, flight of ideas and hyperactivity), b) "excited depression" (depressed mood, inhibition of thought and hyperactivity), c) "unproductive mania" (euphoria, inhibition of thought and hyperactivity), d) "manic stupor" (euphoria, inhibition of thought and apathy), e) "depression with flight of ideas" (depressed mood, flight of ideas and apathy) and f) "inhibited mania" (euphoria, flight of ideas and apathy) (Table III).

The subsequent revisions of Kraepelin and Weygandt of the concept of mixed states partially overcame this tripartite model of the psyche, favouring a dimensional approach that involved a broadening of the concept to the infinite possibilities that a mixture of manic and depressive elements could manifest in the same patient [8]. In their opinion, apart from multiform phenomenal appearances, the essential point for diagnosis of a mixed state was the co-occurrence of manic and depressive elements/symptoms/signs in a patient with clinical features that reflected manic-depressive disorder, and in particular a previous history of manic and depressive episodes (according to Kraepelin, cyclicity – recurrent episodes – defines the illness, irrespective of polarity).

Beyond the six subtypes of mixed states, Kraepelin distinguished between two general classes of mixed states: "transitional" forms, i.e. clinical pictures that frequently arise in the transition from mania to depression and vice versa (reflecting Giesinger's vision of mixed states), and "autonomous" forms, i.e. those that appear and manifest as such (Table II). According to Kraepelin, these "autonomous" mixed states were the most unfavourable ones, presenting with a longer course and the tendency to become chronic [9].

The concept of Kraepelinian mixed states was the object of harsh criticism by other prominent European psychiatrists: Karl Jaspers [10], for example, refused the concept of a mixed state from a methodological standpoint, and Kurt Schneider [11] negated the existence of this diagnostic category, viewing it as a simple transitional phase (from mania to depression and vice versa) in manic-depressive disorder. These are only two examples of the general lack of interest in mixed states that manifested after 1920s, defined by Marneros [9] as the "period of ignorance", evidenced by the dramatic decrease in the number of publications on the subject.

One of the few exceptions was a monograph by the German psychiatrist Mentzos, who utilised some con-

TABLE III.
Kraepelinian Mixed States (1913).

	Mood	Motor activity	Ideation
1. Depressive or anxious mania (*depressive oder angstliche Manie*)	-	+	+
2. Excited depression (*erregte Depression*)	-	+	-
3. Unproductive mania or Mania with thought poverty (*ideenarme Manie*)	+	+	-
4. Manic stupor (*manischer Stupor*)	+	-	-
5. Depression with flight of ideas (*ideenfluchtige Depression*)	-	-	+
6. Inhibited mania (*gehemmte Manie*)	+	-	+

cepts from Weygandt and proposed a new classification of mixed states. Building upon the static conception and clinical descriptions of Kraepelin and Weygandt, Mentzos added a dynamic view. In fact, the classification of Mentzos referred to a psychopathological model which was not based on the description of a clinical picture as a group of different symptoms; indeed, the mixed state was interpreted using the so-called "mood boost" system. According to this view, mood alterations in bipolar disorder could be seen as pathological variations of the "boost", or as the underlying force behind psychic processes, and "mood" as the prevalent affective tone that "colours" thoughts of consciousness. In this model, mania and depression are seen as concordant alterations of boost and mood (increased energy and euphoric mood vs. decreased energy and depressed mood), while mixed states are viewed as discordant alterations (e.g. increased energy and depressed mood). Mentzos used a bipartition between "mixed states" where the deviations in boost and mood were discordant but stable, and "mixed pictures", where they were discordant and, importantly, variable over time (unstable). Unfortunately, due to the complexity of this psychopathologic model, clear criteria for the identification of mixed states were not proposed, and the terminology adopted was difficult to translate in the international nomenclature [12].

The revival of mixed states (what Marneros calls "the renaissance" of mixed states) started from the beginning of the 1980s, the initial stages of which can be seen in the "Vienna Criteria" [13], named after the city from which the authors originated. The Vienna School, in the wake of Mentzos, divided mixed states into two subtypes, stable and unstable, and proposed precise diagnostic criteria for the identification of both (Table IV). These criteria were based on a well-defined psychopathological model known as Janzarik's concept of structural-dynamic coherence [14]. According to this model, similar to the idea of Mentzos, mixed states were perceived as the product of unstable alteration of the "dynamic". The term dynamic referred to the mixture of two components that normally form the individual's personality: one that constitutes the functional substrate of the temperament and a "structural" form that encodes both innate and acquired behavioural patterns. A strict adherence to this model, which is provocative and challenging, limited the use of the Vienna Criteria to research purposes. Nonetheless, these criteria represented a turning point that influenced and stimulated research in the forthcoming years, giving rise to a large number of publications, especially in the US and Europe. Among these, Akiskal in the US and Koukopoulos in Italy, greatly contributed to the so-called renaissance or revival of mixed states [15]. Akiskal postulated that mixed states are not a mere overlap of depressive and manic opposite symptoms, but rather that they arise from the combination of an affective episode with a dominant temperament of opposite polarity; mixed states may arise: 1. when a temperament intrudes into an affective

TABLE IV.
Vienna school criteria for stable and unstable mixed states (from Berner et al., 1983, modified).

Unstable mixed states	
A.	Appearance of at least one of the following rapidly cycling changes following a period of normal functioning: 1. mood changes rapidly cycling from depression and/or anxiety, euphoric/expansive hostile mood 2. rapid cycling and exaggerated emotional resonance in various affective states (depressive, anxiety, manic and hostile) 3. rapid cycling between inhibition, agitation, increase in drive and occasional aggressiveness
B.	Biorhythmic disturbances* 1. diurnal variations of affectivity, emotional resonance, or drive 2. sleep disturbances (interrupted, prolonged, or shortened sleep or early awakening)
Stable mixed states	
A.	Appearance of persistent variations in affectivity, emotional resonance or drive after a period of normal functioning (requires symptoms 1 and/or 2 and 3): 1. depressed, anxious, euphoric/expansive or hostile mood 2. lack of emotional resonance or limited to depressive, manic, hostile or anxious response 3. persistent presence of drive in contrast with the affective status and/or emotional resonance
B.	Appearance of biorhythmic disturbances* 1. daily changes in affectivity, emotional resonance, or drive 2. sleep disturbance (interrupted, prolonged, or shortened sleep or early awakening)
* Symptoms 1 and 2 are required.	

episode of opposite polarity (e.g., depressive temperament into mania or hyperthymic temperament into major depression), or 2. when the instability of a cyclothymic temperament transforms a major depression into a mixed picture [16]. Koukopoulos, on the other side, contributed to the understanding of agitated depression as a mixed state, and challenged the notion of polarity as the basic criterion for bipolar disorder [17]. He defined "mixed depression" a depression occurring with excitation, meaning manic symptoms (like flight of ideas or talkativeness), but also agitation, irritability and rage, marked anxiety and suicidal impulsivity. Koukopoulos considered this highly agitated and tense depressive state as the opposite of melancholia, which is markedly psychomotor retarded and not irritable or rageful. Unfortunately, Koukopoulos' view was not fully endorsed in tge DSM-5.

Mixed states in DSM-IV-TR

Mixed Mania

In the scientific literature there is no univocal definition for mixed mania, also known as depression during mania or dysphoric mania, and the clinical presentation has been described in several different ways. The classic definition includes the presence of a complete manic syndrome together with the presence of at least three depressive symptoms, but, using a more unrestricted approach based on the presence of two depressive symptoms, the frequency of the diagnosis of mixed mania significant increases. Compared to non-mixed episodes, the symptomatology of mixed manic episodes includes the presence of a greater mood lability and irritability, dysphoric mood, anxiety, suicidality and cognitive impairment. On the other hand, these patients report less severe typical manic symptoms, such as euphoria, grandiosity, decreased need for sleep and involvement in pleasant activities. Frequently, the most severe forms are characterised by the presence of psychotic symptoms, such as delusions, hallucinations and motor disturbances that make it difficult to differentiate these forms from schizophrenia and other psychoses [18].

Mixed depression

In the same way, a consistent number of depressed patients show manic symptoms, without a clear, univocal definition for this condition called mixed depression, also known as agitated depression or dysphoric depression. The frequency of this form is variable ranging between 20 and 70%, and this wide fluctuation mainly depends on the different tools used for the assessment of affective symptomatology. The classic definition includes the presence of a complete depressive syndrome together with the presence of a minimum of two or three manic/hypomanic symptoms. Psychomotor agitation is required for the diagnosis of agitated depression. Compared to non-mixed episodes, the symptomatology of mixed depressive episodes includes the presence of a greater irritability and mood lability associated with mental and psychomotor overactivity, restless agitation and increased suicidality [19].

Mixed states in DSM-5 and ICD-10

Both the American Psychiatric Association classification system (the *Diagnostic and Statistical Manual for Mental Disorders* - DSM, now in its fifth edition) [20] and the World Health Organization (*International Classification of Diseases* - ICD-10) [21] provide a definition of mixed states far from the richness and multiplicity of psychopathological descriptions reviewed in the previous paragraphs. The DSM classification, however, made significant changes in the description of mixed episode from DSM-IV-TR [22] to the new "with mixed features" specifier in DSM-5.

According to DSM-IV-TR criteria, it was only possible to diagnose a mixed episode if the criteria for both a manic and a major depressive episode (except duration – only one week was required) were met. In the ICD-10, the term "mixed episode" indicates the co-occurrence or rapid cycling of prominent depressive and manic or hypomanic symptoms for at least 2 weeks. The 11th revision of the ICD will likely revise the concept of mixed episode following DSM revision. The two classification systems simplified the concept of "mixed states" and grouped them into a single diagnostic category (mixed episode); this simplification, however, brought about a series of problems, especially in terms of sensitivity in revealing psychopathologic symptoms that the majority of clinicians would judge as belonging to that category, but which do not reach sufficient threshold criteria to make a diagnosis.

Considering the DSM-IV-TR, the possibility that mixed states can coexist in the context of type II bipolar disorder was excluded, contrary to common experience in clinical practice. Moreover, the definition of mixed episode as the coexistence of full depressive and manic episodes meant that the presence of few symptoms of opposite polarity in the context of predominant manic or depressive episode was not considered. A third limitation of the DSM-IV-TR criteria for mixed episode was the exclusion criterion C: "the symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hyperthyroidism)"; affective episodes temporally correlated with the use of substances (drug of abuse, antidepressants, somatic therapies) and with prominent mixed features are, on the contrary, very common in clinical

practice and could not be correctly recognised and diagnosed according to DSM-IV-TR criteria [23].

The major limitations in ICD-10 criteria concern the low precision and reliability of the diagnostic definition itself, since the number of symptoms needed for the diagnosis is not specified. A second limitation of ICD-10 criteria is the poor sensitivity relative to temporal criteria: ICD-10 requires a duration of two weeks, which is considered to be excessive [24].

In the DSM-5, a revision was made on criteria for mixed episodes: the new criteria have replaced the category "mixed episode" (extremely narrow definition of mixed states) with the specifier "with mixed features" (broad definition). The new classification will capture subthreshold, non-overlapping symptoms of the opposite pole using the new "with mixed features" specifier to be applied to manic episodes in bipolar I disorder (BDI), hypomanic and depressive episodes experienced in BDI, BD type II and major depressive disorder. In the new mixed categorical-dimensional concept used in the DSM-5, the mixed features specifier: 1) would apply not only to manic episodes (as in the DSM-IV), but also to hypomanic and major depressive episodes (even in a MDD longitudinal diagnosis), and 2) broadens the concept of mixed episodes as the threshold for the diagnosis is lowered to ≥3 symptoms of opposite polarity. It is evident that these new criteria have introduced considerable changes to the diagnosis of mixed states, which are in agreement with many of the aforementioned studies.

The current DSM-5 definition replaced the diagnosis of "mixed episode" with a "mixed-features specifier" which should be applied to episodes of major depression, either hypomanic or manic, together with, or in close juxtaposition, with at least three symptoms of opposite polarity. The mixed features specifier may be considered when patients with manic or hypomanic symptoms show at least three depressive symptoms and, conversely, if a depressed patient shows manic or hypomanic symptoms. Patients meeting criteria for mania and depression (the mixed episode of DSM-IV-TR) in the DSM-5 satisfy the criteria for "mania with mixed features", highlighting the greatest functional compromise and clinical severity of mania over depression [20].

The ICD-11 criteria will be substantially similar to those of the DSM-5, with the difference that the term "mixed episode" will be maintained and further divided into six subtypes depending on the current predominant episode and presence of psychotic symptoms [25]. For example, the possible diagnoses will be "actual mixed episode, current mania with depressive symptoms, psychotic (or non-psychotic)"; a similar scheme will be used for hypomanic and depressive episodes.

Epidemiology

The diagnosis of mixed affective states represents a challenge for clinicians for the different definitions and the frequency of mixed and non-mixed manic subtypes, which are mainly dependent on setting, interview methods, assessment and criteria adopted. This problem is the main cause of the differences of prevalence rates found in the different studies. Akiskal [26] stated that mixed states are a common presentation of BD, but a careful evaluation highlights large differences among mixed manic or depressive states and a huge variability linked to the criteria used for the evaluation.

For mixed manic states, the prevalence rates are usually lower when adopting the ICD-10 and DSM-III/IV criteria, ranging from 19% (ICD 10, 33) to 6.7-28% [27 28]. Prevalence rates of mixed depressive states are somewhat scarce and the variability for manic mixed state is similar to that found for mixed depressive states. Indeed, across studies, the differences fluctuate between 20 and 70%, and the frequency of mixed and non-mixed depressed subtypes is mainly dependent on setting, interview methods, assessment and criteria used [29]. Data on gender generally demonstrate the presence of differences between subtypes, confirming the presence of a female predominance in the mixed manic state ranging from 63 to 69% and the absence of gender differences in the prevalence of mixed depression [30].

Treatment

The pharmacological treatment of mixed bipolar states remains a challenge for clinicians. Results from studies and clinical practice show that mixed presentations in bipolar disorder have a poorer pharmacological response compared with pure episodes, and combination therapy is often required [31 32]. An additional challenge in the treatment of mixed states arises from the need to concurrently treat both manic and depressive symptoms: depressive-switch risk often may derive from an antipsychotic monotherapy centred on improving manic symptoms [33], particularly in the case of conventional antipsychotics and other drugs with a high polarity index [34]. Conversely, antidepressants can induce a manic/mixed switch [35]. The lack of standard definitions of mixed states, the low reliability of assessment measures and the DSM-IV-TR definition (considering mixed episodes as variants of mania) are further potential reasons for the lack of adequate research in this area. The majority of data is derived from post-hoc analyses of studies including manic patients and from a handful number of double-blind, placebo-controlled studies [36]. Combinations of atypical antipsychotics and conventional mood stabilisers, particularly divalproate, have the most consistent evidence [37].

Even if most second generation antipsychotics (SGAs) have been approved for the treatment of mania, only a few guidelines make specific recommendations for managing mixed episodes, given the paucity of evidence-based data [32]. Available data show that asenapine, olanzapine and valproate have positive effects in patients with mixed mania in placebo-controlled trials [38-40], and aripiprazole and ziprasidone show separation from placebo in pooled analyses [41 42]. There are a few positive data on the use of quetiapine in acute mixed states [43]. Ziprasidone has been tested in depressive mixed states [44]. Asenapine and olanzapine have shown positive effects in combination with valproate in patients with mixed mania. The guidelines of the *World Federation of Societies of Biological Psychiatry* [45] recommend lithium in pure euphoric mania rather than in mania with dysphoric or depressive symptoms, while carbamazepine is suggested for mixed states or dysphoric mania, and valproate for both manic/depressive dysphoric features during a manic episode. Among typical antipsychotics, haloperidol may exacerbate depressive and dysphoric symptoms in mixed mania. The guidelines of the *British Association for Psychopharmacology* (BAP) [46] recommend oral administration of antipsychotics or valproate as first-line treatments for severe mixed episodes, in patients not already on long-term treatment. The CANMAT and ISBD treatment guidelines [40] suggest aripiprazole, paliperidone ER, olanzapine and asenapine monotherapy as first-line choice in mixed mania. The NICE guidelines suggest that patients with mixed states should be treated as if they have an acute manic episode, and no antidepressants should be prescribed.

Data on the use of SGAs in the treatment of acute mixed episodes are limited, both in monotherapy and in combination. In one randomised trial of a mixed episode cohort, Houston et al. [47] reported earlier reduction of both manic and depressive symptoms of mixed episodes in patients treated with adjunct olanzapine over a 6 week period compared to adjunct placebo.

Muralidharan et al. [48] published the first meta-analysis of all randomised double-blind placebo-controlled clinical trials on the efficacy of SGAs (as monotherapy or in combination with mood stabilisers) in treatment of mixed episodes, according to the DSM-IV criteria. The meta-analysis showed that SGAs in combination with mood stabiliser were superior to placebo plus mood stabiliser. The authors specified that SGAs were superior to placebo in the treatment of mixed episodes, particularly for manic symptoms, while moderately effective in reducing depressive mixed symptoms. Nonetheless, the interpretation of results should take into consideration that clinical trials included patients experiencing mixed episodes as defined in the DSM-IV, which considers mixed episodes as a type of mania. The DSM-5 has eliminated mixed episodes as a category, while including mixed features as a course specifier for both manic and depressive episodes. The results of this meta-analysis suggest that SGAs are clearly effective in treating manic symptoms in mixed episode patients with syndromal mania and syndromal depression. However, findings on depression are limited and further studies are needed to establish the efficacy of SGAs in treating depressive symptoms in manic patients with mixed features.

Ouanes et al. [49] in a recent review demonstrated the overall efficacy of SGAs in mixed episodes. Antidepressant use is perhaps the most controversial issue in the treatment of bipolar disorder and the scientific literature is limited and controversial [50]. Some studies support that the adjunctive use of antidepressants is not associated with an increased risk for switching to mania/hypomania or mixed episodes [51], but others are at odds with these findings [52], showing that antidepressants do not significantly increase the rate of enduring recovery from depression in bipolar I and II disorder. Nevertheless, there is a substantial consensus on avoiding antidepressant monotherapy in bipolar patients with mixed/cycling features or prior antidepressant-associated mania/hypomania [53]. International guidelines give heterogeneous recommendation and take into consideration two potentially harmful effects of antidepressants, including the induction of hypomania/mania or mixed episodes and rapid cycling. However, a consensus exists in stopping the ongoing antidepressant medication during a mixed episode in both bipolar I and II patients [54].

Conclusions

Bipolar disorder has been the subject of significant revisions in the DSM-5. One of these major changes has been the removal of BD from the 'Mood Disorders' section and its inclusion in the new category of 'Bipolar and Related Disorders'. Another significant change concerns mixed states: the diagnosis of "mixed episode" has been replaced with a "mixed-features specifier" which should be applied to episodes of major depression, either hypomanic or manic, together with, or in close juxtaposition, at least three symptoms of opposite polarity. The mixed features specifier may be considered when patients with manic or hypomanic symptoms show at least three depressive symptoms and, conversely, when depressed patients show manic or hypomanic symptoms. Patients meeting criteria for mania and depression (the former mixed episode of DSM-IV-TR), will receive the DSM-5 diagnosis of "mania with mixed features", emphasising the greatest functional compromise and clinical severity of mania over depression.

The revival of the concept of mixed states will be hopefully fostered by changes in the DSM-5 definition, and is also a consequence of the renewed interest on this subtype of bipolar disorder. Of course, the current criteria of mixed states are not equivalent to the classical, Kraepelinian notion of mixed states and could have been improved. Both DSM-IV-TR definition of mixed states and the DSM-5 mixed features specifier show clear troubles, in particular in recognising severe mixed states, while the combinatory model shows a greater sensitivity for the definition of less severe varieties of mixed states characterised by clearly identifiable symptoms. Moreover, the mixed categorical-dimensional concept used in the DSM-5 does not adequately reflect some overlapping mood criteria, such as mood lability, irritability and psychomotor agitation, considered among the most common features of mixed depression. The significant changes made in the DSM-5 will help researchers in studying the clinical characteristics of this subtype of bipolar disorder and in implementing effective treatment strategies. Guidelines for the treatment of mixed states, in fact, do not give clear indications for pharmacological or non-pharmacological treatments of mixed states, and the few available data are limited to post-hoc analyses and subanalyses performed in bipolar, mostly manic, patients.

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The psychopathological characteristics of prolonged grief

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Summary

Grief is a normal human response to the death of a loved one that may vary among individuals and in the way it manifests itself across cultures. Whereas the majority of bereaved people adjust adequately to the loss, a small but noteworthy proportion of individuals may experience a prolongation of the symptoms of acute grief well beyond the period when these have commonly abated. This syndrome, characterised by prolonged psychological distress in relation to bereavement, has been termed prolonged grief (PG) and shows distinct psychopathological features compared with other stress-related mental disorders. Accurately diagnosing PG in the context of difficult bereavement is an ongoing challenge to clinicians and researchers and many have called for improving the identification of PG and its treatment. PG has been recognised as a predictor of negative outcomes, such as substantial impairment in work and social functioning, reduction of quality of life, risk for mental disorders and suicidality, and physical health problems. This article discusses the main clinical features of PG, the determinants associated with the severity of PG symptoms, the risk factors that may predispose an individual to develop PG and the efficacy of different preventive and treatment approaches, including psychopharmacological and psychotherapeutic interventions.

Key words

Bereavement • Grief • Complicated grief • Traumatic grief • Prolonged grief disorder • Prolonged grief diagnostic criteria • Prolonged grief risk factors • Prolonged grief treatment

Introduction

Over the last 20 years, several studies have focused on complications of grief and bereavement [1 2]. Assuming that bereavement is a normal human experience and that grief is the physiological reaction to the loss of a loved one, many researchers have attempted to identify the stages of grieving process as well as the order in which they may arise. Historically, Kübler Ross described grief as a succession of five steps according to a relatively linear "recovery" trajectory over time (the so-called five-stage model) [3]. Recently, it has been showed that bereaved people, in correlation with different individual and contextual features, may experience a range of symptoms during the whole process, and not necessarily in a sequential order [4]. Empirical data have indeed supported the existence of distinct patterns of grieving, allowing recognition and study of different trajectories of the process [5 6].

Evidence has demonstrated that most bereaved individuals finally succeed in coming to terms with the loss of their loved one and integrate this experience in their lives [1 4 5]. The time period during which this process is completed has not been definitely established, but most experts agree that progress usually becomes apparent by 6 months. Even if possible intense symptoms may re-emerge periodically, most people are able to adjust to the loss by this time [7-10]. Unfortunately, a small subset of bereaved individuals never fully integrates the loss into their life, and continue to experience severe disruption in daily life even many years after the loss.

The labels given to this condition have changed over the years, including pathological grief, traumatic grief, complicated grief and, more recently, prolonged grief [10]. We decided to use the term "prolonged grief" (PG) for two reasons. First, it better expresses the nature of the disorder, characterised by the abnormal persistence of severe disabling symptoms related to the bereavement [11]. Second, it is most likely that the revision of the International Classification of Disease (ICD-11), which is currently planned for approval by the World Health Assembly, will introduce a new diagnosis to recognise this clinical condition, using the label of Prolonged Grief Disorder (PGD) [12].

However, the identification of this syndrome in the current psychiatric diagnostic systems has been much debated recently. Factor analytic studies have identified and isolated the specific PGD symptoms, indicating that it is

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distinct from other psychiatric disorders, such as anxiety, depression, post-traumatic stress disorder and adult separation anxiety [13-16]. Based on these data, consensus criteria for PGD have been formulated [10]. Nevertheless, the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), failed to include this diagnosis, relegating the complications of grief to the section "other specified trauma and stressor-related disorders", under the label of *Persistent Complex Bereavement Disorder* (PCBD), with the explicit criteria listed under conditions requiring further study [17]. The DSM-5 reluctance to recognise PGD as a full diagnosis is probably due to different reasons, such as the risk to pathologise normal grief responses, the risk to underestimate the influence of cultural and contextual variables on the variation of the manifestations of grief and the risk to place much emphasis on traumatic stress, which may result in misdiagnosing or not diagnosing individuals suffering from other common and severe mental disorders [12 18 19].

Contrary to DSM-5, the ICD-11 will likely include, within the proposed new group of "Disorders specifically associated with stress", a separate diagnosis of PGD, as a condition characterised by a distinct psychopathology [12]. The ICD Working Group has exposed different elements favouring the inclusion of this new diagnosis. First, studies have shown that the core symptoms of PG are distinguishable from symptoms of uncomplicated grief [13 20] and are associated with significant consequences. In fact, PG can predict long-term functioning impairments, reduction of quality of life, risk for mental disorders and suicidality, as well as physical health problems (e.g. hypertension, cardiovascular disorders, immunological dysfunctions) [9 14]. Second, the risk of medicalisation of some non-pathological reactions of grief seems very limited: epidemiological data show that a PG diagnosis only applies to a minority (about 10% following normal circumstances of loss) of bereaved people who experience persistent impairment [10 21], with higher rates following disasters, violent deaths, or the death of a child [22-24]. Moreover, population rates of PG are estimated between 2.4% and 4.8% [25 26]. Finally, diagnostic requirements have been also drawn carefully taking into account the marked cultural variations in the manifestation of grief. Although more research is needed in this area, some studies have shown that PG is present across a range of cultures, including non-Western settings, as well as across the life span [22 27 28].

Controversies aside, a growing literature has outlined PGD as a nosological distinct entity, characterised by distinctive phenomenology, risk factors, aetiology, different response to treatment and adverse outcomes [10 29]. In this paper, we aim to clarify psychopathological characteristics of PG in order to facilitate clinicians in identifying bereaved individuals who suffer from the syndrome and provide them with appropriate, timely and effective treatments.

The phenomenology of prolonged grief

According to the model proposed by Prigerson et al. [13], PG includes two core clusters of symptoms: the first is related to separation distress (e.g. intensive yearning, strong desire of the beloved, constant state of concern linked to the memory of the loved one), and the second is related to traumatic distress (e.g. recurrent and intrusive thoughts about the absence of the deceased, sense of disbelief regarding the death, being angry or emotionally numb, tendency to avoidance of memories associated with the pain of loss) [10]. Bereaved people who suffer from PG typically have difficulty in accepting the reality of the death and in adapting to life without the deceased. They find themselves in a repetitive loop of intense yearning and longing, being unable to move forward in life. PG symptoms last over 6 months, can sometimes persist for years and negatively influence functioning and quality of life [14]. PG symptoms also include anger, guilt, or blame regarding the death, lowered self-worth, inability to form new bonds or relationship with others and strong denial of the loss, which is accompanied by feelings of mistrust, bitterness and identity confusion [10 29]. Overall, a significant preoccupation with the deceased is developed, with ruminations about circumstances or consequences of the loss, intense physical or emotional reactivity to reminders, avoidance of reminders, or compulsive proximity seeking (e.g., keeping reminders of the died person). This condition can lead bereaved individuals to be chronically disengaged from others and from the world, to believe that life is empty and meaningless without the deceased and that their intense pain will never end. For this reason, suicidal thoughts may occur and are usually related to the hope of being reunited with the deceased loved one [8 30].

Some years ago, a panel of experts on bereavement approved a consensus list of shared symptoms, outlining the clinical features of PG. They proposed empirically a final diagnostic criteria set: bereaved individuals with PGD must experience yearning (i.e. physical or emotional suffering due to an intrusive unfulfilled desire for reunion with the deceased) and at least five of nine additional symptoms. The latter must persist for at least 6 months after the bereavement and be associated with functional impairment [10]. Factor analysis studies have contributed to define the nature of PG and underlined its clinical meaningful dimensions. In a large sample of patients, using the 19-item *Inventory of Complicated Grief*, six clusters of symptoms were identified: "yearning and preoccupation for the deceased", "anger and bitterness", "shock

and disbelief", "estrangement from other", "hallucinations of the deceased" and "behaviour change, including avoidance and proximity seeking" [19]. These factors did not perfectly align with those reported in a subsequent study, which examined the factor structure of PG using the 31-item *Structured Clinical Interview for Complicated Grief* and found five explanatory factors: "yearning and emotional pain", "difficulty accepting the death", "emotional numbness, loneliness and social disconnection", "suicidal ideation and meaninglessness", "avoidance and negative affect" [17]. Although direct comparison is hampered by methodological differences, including the quite high rates of comorbidity with other mental disorders, the findings of the two studies have some overlap. We note, for example, that in both cases yearning is indicated as first factor, confirming the centrality of this element in the disorder. The factor analysis studies, integrating clinical insights with empirical data, have contributed to determining the constitutive symptoms of PGD, delineating it as a mental disorder that is distinguishable from other mental disorders such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) [13 15 31]. However, some PGD symptoms do overlap with some symptoms of MDD and PTSD, and comorbidity of PGD with MDD is not uncommon [32 33]. Indeed, 50-60% of PG individuals also meet criteria for a major depressive episode [26 32]. Likewise, some evidence has shown that pre-existing depression may predispose individuals to develop PG after the loss of a beloved one [6]. Therefore, it may be difficult for clinicians to make a diagnostic distinction between these clinical conditions.

How to distinguish PGD from MDD

PGD and MDD both include symptoms such as sadness, crying, sleep disturbance and suicidal thoughts. However, several studies have shown important differences between the two disorders. First, they have a different aetiology. Whereas PGD specifically arises as a result of a loved one death, MDD can result from many causes and, in some cases, may even arise without a clear cause [5 19]. Regarding symptomatology, PGD symptoms are more stable over time than MDD ones. Bereaved individuals with PGD experience a consistent yearning, while MDD does not typically involve yearning. Factor analysis studies have confirmed that yearning loads highly on a grief factor, but not on depression. On the contrary, sadness loads highly only on a MDD factor [13 34]. A study on negative cognition among bereaved people have found that "being overwhelmed by the loss" is specific for PGD, but not for depression, and that they show loss-related avoidant behaviours, while MDD is characterised by a more global avoidance [35]. Likewise, PGD may include feelings of survivor guilt, which is specifically death-related, whereas depression guilt is usually pervasive and multifaceted [19]. In addition, suicidal thoughts are different: in PG they are most commonly based on the strong desire to reunite with the loved one, whereas depressed people tend to attribute them to pervasive hopelessness [19].
Moreover, the two conditions are different in clinical correlates. In fact, some evidence suggests that PG is not associated with a change in electroencephalographic (EEG) sleep physiology seen in MDD [36]. In a more recent study, it has been demonstrated that bereaved PGD patients present activation of dopamine circuits and reward-related neural activity in the nucleus accumbens in response to reminders of the deceased, while depressed ones have a reduced capacity of activation of the same pathways [37].

How to distinguish PGD from PTSD

Experiencing the death of a loved one may be a traumatic life-changing event. Both related to this severely distressing identifiable event, PGD and PTSD share some similarities, such as symptoms of emotional numbing, disruptive intrusive thoughts, avoidance, inability to function and difficult reintegration into society [19 29 38]. However, several studies have shown that most individuals with PGD do not meet criteria for PTSD [31 33 39 40]. In fact, phenomenological differences between the two disorders have been detected. First, the hallmark of PTSD is fear, while the dominant emotions associated with PG are yearning and sense of emptiness [29 30]. Even when PTSD arises after a loss of a loved one, intrusive thoughts are fixated on the death event itself, whereas in PG bereaved individuals experience intrusive and voluntary thoughts about diverse aspects of the relationship with the deceased. Indeed, they do not show typical symptoms, such as flashbacks, nightmares, vivid intrusive recollections of the event [5]. Although both disorders are characterised by memories that are maintained permanently over time, the emotional valence of the contents is different: negative for PTSD and bittersweet (negative and positive, often concurrently: the memories of the deceased may provide comfort, but can also stimulate pain as a reminder of what is lost) for PGD [30]. In PTSD, the traumatic event generates a sense of threat and leads individuals to avoid internal and external reminders of the death, whereas in PGD avoidance is consequently limited to those stimuli that serve as reminders of the reality or permanence of the loss. Moreover, hyperarousal symptoms in PTSD are frequent and are related to hypervigilance to threat, whereas in PGD they are rare and related to the loss of interpersonal regulators [19].
Sometimes the differences between PTSD and PGD may appear less evident, for example when the deceased one is a child or a victim of major disasters. In these cases, the feelings of injustice and anger over the cir-

cumstances of the death may be overwhelming, leading to a more severe grief and psychopathological status [30]. However, a recent study conducted on 643 survivors from the Asian tsunami has confirmed that PGD is distinguishable from PTSD. In details, bereaved individuals with PGD have obtained significantly lower scores on avoidance, hyperarousal and intrusion at the *Impact of Events Scale-Revised*, compared to those who were experiencing PTSD symptoms [22].

Risk factors of prolonged grief

Several studies have focused on possible risk factors for PGD [41-43]. In a multicentre US study, 19 possible risk factors were evaluated by administering the *Bereavement Risk Questionnaire* to 262 hospice coordinators. Professionals identified bereavement risk factors, such as perceived lack of caregiver social support (70%), caregiver history of drug/alcohol abuse (68%), caregiver poor coping skills (68%), caregiver history of mental illness (67%) and patient is a child (63%) [41]. More recent studies have confirmed a specific role of these determinants, and have identified other factors that may predispose an individual to develop PGD, such as female gender, low education, older age, low socioeconomic status and low social support both before and after the death [43 44].

Research has also focused on the types of the relationship to the deceased, underlining that attachment issues are salient in creating a vulnerability to PG. There is a substantial evidence that individuals with PG have experienced a close kinship relationship with the deceased. The reason why the loss is particularly devastating is harbouring precisely to the perception that the relationship was satisfying, life affirming and identity-defining [45]. Examining the correlation between marital quality and adjustment to the impending loss of a terminally ill spouse, it was suggested that security-increasing marriages and insecure attachment styles put spouses at risk for elevated prolonged grief symptoms [46]. Moreover, emotional dependency on the dying patient was found associated with grief, but not with depressive symptoms [47]. In the Japanese general population, alexithymia has been shown to contribute strongly to depression, but not to PG [48]. On the contrary, childhood separation anxiety was significantly present in the history of those who develop PG, but not in other disorders, such as MDD, PTSD or generalised anxiety disorder (GAD) [49]. Regarding avoidant attachment styles, contradictory results have emerged: some authors have pointed out a positive association between neuroticism, anxiety and avoidant attachment with PGD severity [50], while others have shown data supporting the thesis that avoidant attachment, if associated with low anxiety levels, may promote a marked reduction of PG symptoms [51].

Although the nature of the relationship is the most important variable for developing PG, the circumstances of the death can also play a role. Studies have confirmed that traumatic features of the death (e.g. sudden, violent, unexpected death), a lack of preparation, or difficult interactions with medical or other staff at the time of the death may predispose to PG [4 10]. Loss of a child is also recognised as a powerful risk factor for PG [52].

A higher risk of PG is found in cancer patients' caregivers who report a perceived general disapproval from others, longer duration of caregiving, and own medical disease history [44 53]. In a prospective longitudinal study with 342 cancer patients' caregivers, hospital deaths were associated with a heightened risk for PGD (21.6% *vs* 5.2% $p = 0.02$) compared with home hospice deaths, which may instead have a reduced risk [44].

Another important factor associated with PG is a previous psychiatric history of depression, anxiety or bipolar disorder, as well as a history of multiple trauma or losses [47 54]. On the contrary, several investigators have found that spiritual belief systems may decrease the risk of developing PG [55]. Regarding ethnicity, a small cohort study has reported interesting results: African Americans have a 2.5 times higher incidence of PGD than the Caucasian population [27]. Further research is, however, needed on this issue.

Some recent studies have pointed out that psychometric scales, developed for the evaluation of symptoms of PG in the period preceding the death of their loved one, can be useful in predicting subjects at higher risk of post-loss PG. For example, in a palliative care setting, a higher score at the *Complicated Grief Inventory* (CGI pre-loss) was significantly associated with a PG diagnosis after the loss [56]. Similarly, the *Prolonged Grief-13* (PG-13), a validated risk assessment screening measure for PG, was useful in identifying people at high, moderate or low risk of developing PG after the death of their beloved [57]. These data may have important clinical implications, prospecting the possibility to detect the population at risk for PG and to offer them interventions as early as possible.

The treatment of prolonged grief

Several studies have demonstrated that PG has a different course and response to treatment compared with normal grief and depression. Despite this, pharmacological trials in PG are scarce. Historically, the prescription of tricyclic antidepressants to bereaved individuals have been shown to be useful to improve depressive symptoms, but appeared less effective than placebo in ameliorating specific PG symptoms [58 59]. More recent studies have indicated that dopamine reuptake inhibitors may induce only a moderate response [45], whereas selective serotonin reuptake inhibitors have shown significant improvements on PG symptoms [10]

[60]. A significant reduction of the intensity of grief (48% of the mean score at ICG) and of depressive symptoms (51% of the mean score at HDRS rating scale) was found after administration of paroxetine (10-50 mg per day) to a small group of PG individuals [58]. In a case-series of four women with a primary diagnosis of PG, Simon et al. found a 76% improvement in grief symptoms at ICG when prescribing 10 mg per day of escitalopram [61]. The efficacy of escitalopram (10-20 mg/per day) on specific PG symptoms was confirmed in a subsequent trial [62]. However, considering the limited pharmacological research trials, the optimal first-line treatment for PG is a therapy-based approach, with medications used as add-on if needed [63].

Several preventive intervention programs have been proposed to enhance adaptation to bereavement and reduce grief symptoms in order to prevent complications and mitigate long-term negative consequences of bereavement. Unfortunately, a meta-analysis examining the results of nine randomised controlled trials on preventive interventions to bereaved individuals at risk to develop PG did not show any effectiveness of these interventions [64]. This finding was confirmed in a more recent review: the authors have also argued that such interventions may even interfere with the "natural" grieving process [65]. Nevertheless, some interesting data come from a recent study on an Internet-based therapist-assisted cognitive-behavioural intervention as a prevention measure of PGD in recently bereaved individuals, called *Healthy Experiences After Loss* (HEAL). This intervention was shown to be well-tolerated and effective in reducing the burden of significant pre-clinical PGD. Although further research is needed, the preliminary results look promising [66].

Moreover, psychotherapy specifically designed for PGD (named *Complicated Grief Therapy* - CGT) has been shown to be beneficial [67]. This new psychotherapeutic model, drawn from attachment theory and with roots both in interpersonal and cognitive-behavioural therapy, includes a variety of loss- and restoration-focused techniques. It also includes techniques similar to prolonged exposure, which reduce PG severity, by promoting emotional processing of memories of the death [11]. Shear et al. compared CGT with standard *Interpersonal Psychotherapy* (IPT) in a randomised trial with PG individuals. Higher response rates (51% *vs* 28%) and faster time to response were detected in the CGT group [68]. In a recent replication and extension of the study, these findings were confirmed demonstrating that CGT, compared with IPT, conferred higher symptom reduction, faster response rate (70.5% *vs* 32.0%) and a greater persistence of the results at 6-month follow-up (100.0% *vs* 86.4%) [69].

Conclusions

Experts in the field of bereavement agree in recognising PGD as a new diagnostic entity to be included in current psychiatric diagnostic manuals. PGD is in fact characterised by distinctive phenomenology, aetiology, risk factors, response to treatment and adverse outcomes. The current literature reveals significant advancements in research regarding this condition with important clinical implications. Healthcare professionals may favour early identification of the subset of individuals at risk for PGD, thus reducing the psychological impact of modifiable risk factors and providing them with an adequate psychosocial support. Furthermore, agreement on standardised criteria for PGD will allow clinicians and researchers to identify bereaved individuals who have developed PGD, directing them to specific treatments and preventing negative consequences. The need for further studies, especially double blind, randomised, placebo-controlled trials, is urgently needed in order to identify the most effective treatment modalities.

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Relationship of non-suicidal self-injury and suicide attempt: a psychopathological perspective

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Summary

Non-suicidal self-injury (NSSI) is not uncommon in the general population, and is prevalent in association with a range of psychiatric disorders including major affective, personality and neuropsychiatric disorders. It often starts in childhood or early adolescence and involves repeated bouts of self-injurious acts, with similar risks among females and males. Such behaviours are distinguished from suicide attempts by an evident lack of lethal intent. Nevertheless, NSSI and suicidal behaviours occur frequently in the same persons, and NSSI can be a precursor of suicidal behaviour. NSSI typically seems to represent an effort to reduce overwhelming negative emotions, which can include dysphoric or depressive states. Indeed, the experience of immediate relief may contribute to the repetition of self-injurious behaviours. NSSI may also arise in response to a felt need for punishment or a desire to influence or seek help from others. NSSI behaviours occur far more frequently than suicide attempts, and usually are of low medical severity and rarely fatal. In addition to representing an important psychiatric syndrome in its own right, NSSI is a major risk factor for suicide that requires ongoing assessment of suicidal intent.

Key words

Non-suicidal self-injury • Suicide attempt

Introduction

Nonsuicidal self-injury (NSSI) can be considered as intentional damage of one's body tissue without clear suicidal intent, and usually performed to seek immediate relief of psychic distress [1]. Methods used by 70-90% of persons involve cutting, scratching, or scraping of the skin; less prevalent are banging, bruising and self-hitting in 21-44%, and burning in 15-35% [2]. Other forms of self-injury include biting, skin-picking, wound-excoriation, and uncommon bone-breaking. Most individuals with self-injuries use more than one method [1 2]. It is widely held that NSSI behaviours represent an expression of overwhelming negative emotions, and that they can be important antecedents of suicide [1 3]. The psychological function of NSSI appears to be independent of the self-harm methods employed, although the number of different methods used may predict the level of clinical distress and the potential suicidal risk [1 3].

There are many ways to categorise particular forms of NSSI. One approach is to divide NSSI into major, stereotypic and superficial or moderate types [4]. Major NSSI includes extremely severe self-injurious acts (such as amputation, castration, or eye enucleation), often with the use of an implement; such events appear to be limited to persons with an otherwise diagnosable psychotic disorder. Stereotypic NSSI is more frequent, and is often associated with a developmental disability or neuropsychiatric disorder, usually does not involve the use of an implement, and results in minor, superficial tissue damage; examples include repeated head banging, and biting of the tongue or hands. Superficial or moderate NSSI is most prevalent and includes a range of behaviours involving self-injury with different degrees of severity. Superficial or moderate NSSI can be further divided into compulsive, episodic and repetitive types [4]. Compulsive NSSI includes non-severe ritualistic acts, such as hair-pulling, and is not considered a form of NSSI. In addition, self-injurious acts associated with developmental neuropsychiatric disorders usually are considered different in aetiology and significance from NSSI. Episodic and repetitive NSSI involve similar behaviours, but vary in the frequency of acts. This type of NSSI is the focus of the present report.

NSSI and suicide attempts are dissimilar in their prevalence, evident intent and medical severity or potential lethality. By definition, NSSI is associated with nonlethal intent, and may sometimes function to avoid suicidal urges [5]. Suicide attempt involves lethal intent of varying intensity, although similar distressing affective states may

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be present in both NSSI and suicidal behaviour. In contrast to suicide attempts, medical injuries are typically less severe and rarely life-threatening in NSSI. Compared to suicide attempts, NSSI is not only far more prevalent, but can be performed dozens or even hundreds of times by a single person [6]. Comparisons of NSSI and suicidal acts are considered further below.

We will provide a brief update of recent research on NSSI. Interest in the syndrome has increased markedly since modern epidemiological studies have documented its substantial prevalence in the general population and relative frequency in association with mood, personality and other psychiatric disorders. The inclusion of NSSI in DSM-5 also will be discussed.

Terminology

Historically, there has been confusion in the terminology used to refer to self-harm behaviours. The term self-mutilation was previously used for acts now considered as NSSI, although this term implied major self-injury with loss of the integrity or function of a body-part, such as a limb. The terms deliberate self-harm and parasuicide, as well as self-inflicted violence, self-abuse and even wrist-cutting are ambiguous in including self-injurious acts with or without suicidal intent. In addition, the older term suicidal gesture also is ambiguous about intent, is somewhat judgmental and implies more understanding of motivation than is likely to be known. Clear and consistent terminology and definitions are important both for research and treatment of persons with self-injurious behaviours. Some studies lack close consideration of lethal intent and so may include mixed samples of NSSI and suicidal behaviours [7]. In this overview, with the term NSSI we refer to intentional, physical self-harm without a clear suicidal intent and in contrast to suicide attempts, which involve varying degrees of intent to die.

Diagnostic Issues

NSSI was not included in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) nor in the tenth edition of the International Classification of Diseases (ICD- 10) as a discrete diagnosis, but appeared as a symptom commonly associated with the diagnosis of Borderline Personality Disorder as well as with other psychiatric disorders [3]. In recent years, there have been several proposals to include NSSI as a distinct diagnosis within classification systems [8 9]. Indeed, DSM-5 includes NSSI as a condition that needs further study to support its consideration as a discrete syndromal category, and proposes tentative diagnostic criteria for further discussion, which include: a) the presence of at least five self-injurious acts within the preceding 12 months; b) acts are preceded by negative emotions or thoughts, such as distress, anxiety, sadness, anger, self-criticism, or need for punishment; c) the self-injuries have an apparent psychological purpose, such as to reduce negative emotions or thoughts or to avoid unwanted social situations or consequences; d) the self-injurious acts cause clinically significant social and functioning impairment [10]. Despite its ambiguous diagnostic status, NSSI is clinically important as an indication of functional impairment, its status as a major risk factor for suicide attempts and as a problem requiring specific interventions and management [5 8 11].

Epidemiology

NSSI is an important public health issue. It is a prevalent phenomenon across a range of ages and populations. However, lack of general agreement on its definition and diagnostic criteria limit assessment of its epidemiology and its distinction from suicidal acts. Nevertheless, some information is available about its prevalence in specific age groups and clinical populations. Estimates of its lifetime prevalence range from 0.40-1.0 to up to 2.9% of the general population [1 4 12-14].

Occurrence in young people

NSSI is quite prevalent among adolescents and young adults, and the mean age-at-onset has been estimated at 16 years [1 14]. Rates are somewhat lower among prepuberal children [15], but cases have been identified at 4 years [16]; moreover, 5% of a sample of college students were found to have made self-injurious acts before age 10 [17].

In nonclinical samples of adolescents, 10-15% were found to have self-injured at least once [6, 18-20]. Among adolescents receiving psychiatric treatment, rates of self-injury have been far greater, sometimes over 50%, with more severe, primary psychiatric illnesses [21 22].

Occurrence in adults

NSSI beginning during adolescence often persists into college-age or young adult years, affecting 12-17% of college students [23 24]. In these samples, three-quarters of subjects reported having several episodes of NSSI, starting in late adolescence in approximately 39% of cases. In adults, 46% reported to have had five or more episodes of self-injury [1 14], and the prevalence of NSSI in community samples of adults in the US has been as high as 4% to 6% [1 14 25]. In psychiatric samples of adult patients, the risk of NSSI is as high as 25% [2]. In geriatric samples, rates of NSSI are probably lower than among adolescents and young adults, but estimates are complicated by the rarity of studies in older persons and by confusion between NSSI and suicide attempts at all ages.

In contrast to suicide attempts (predominant in females) and suicide (more frequent in males), sex-differences are minor in NSSI, although women are more likely to engage in cutting behaviours, whereas men are more likely to strike themselves [17].

Relationships of NSSI and suicide

The distinction of NSSI from suicide attempts is not always simple, as suicidal ideation may co-occur with NSSI, and as NSSI is a leading risk-factor for suicide, especially among psychiatric patients and those who have required hospitalisation [26]. A limitation of studies involving self-injurious behaviours is that they usually do not clearly differentiate the presence or level of suicidal intent, which makes it difficult to estimate rates of NSSI versus suicide attempts. Nevertheless, many studies indicate a consistent relationship between apparent NSSI and later suicidal behaviour. The association appears to be independent of sex, age and method of self-injury, and to increase with more frequent episodes of apparent NSSI (especially > 20), a longer history of NSSI, use of multiple (≥ 3) methods of self-injury, a reported lack of pain and of immediate relief of distress after a NSSI act; moreover, some clinical factors, such as severity of psychiatric illness and specifically of depressive features, also increase the association between NSSI and suicidal behaviour [26-29]. A recent study on a large sample of US Army members found that 40% of subjects with NSSI attempted suicide within two years of follow-up [30]. The long-term association of suicide attempts with NSSI may be as high a 70%, with a nearly three-fold greater risk of suicide attempts following a history of NSSI [3 31]. According to Sullivan et al. (2014) [32], there is an increased of NSSI risk in jails. Over the 5 years of their analysis, the total number of acts of NSSI increased by 24%. On the other hand, a few studies have failed to support indications of an association of more severe psychiatric illness among persons who have made self-injurious acts and have also been overtly suicidal [27 33 34].

Importantly, although it is clear that NSSI and suicide attempts are strongly associated [1 26 35], there are also clinically important differences between NSSI and suicide attempts. They differ in psychosocial predictors (in general, NSSI is associated with less depression, anxiety, stress, and suicidal ideation and more self-esteem and interpersonal support compared to suicide attempts) [17 28 36], emotional correlates (relief of discomfort and the experience of positive emotional changes are common in NSSI, whereas depression and guilt often worsen with suicide attempts) [37], motivations (NSSI is usually aimed at generating less abnormal feelings, to punish oneself, or to express anger) [38] and psychological effects [26]. These findings are summarised in Table I.

Psychopathological explanations for the relationship of NSSI with suicide

Spectrum of self-harm

An older view is that self-injurious acts, including NSSI and suicide attempts of varied severity and lethality, form a spectrum of behaviours without sharp distinctions between them [39]. This view has been encouraged by the common association between NSSI and suicide attempts and by the status of NSSI and suicide attempts as the strongest known predictors of eventual suicide [1 7 39 40]. Moreover, NSSI and suicide attempts are associated with similar disorders, particularly depression and personality disorders, so as to enhance their relationship [1].

Acquired suicidal capability theory

In order to end one's own life, an individual has to overcome the fear and pain associated with suicidal behaviour as a means of escaping intolerable psychic distress. One way to increase capability for suicide may be engaging in NSSI behaviour as a means of reducing negative emotions associated with self-harming behaviour and becoming more habituated to, and tolerant of self-inflicted violence [26 41 42].

Gateway theory

NSSI and suicidal behaviour can be considered as existing along a behavioural continuum of self-harm behaviour, ranging from NSSI to completed suicide. NSSI may precede the development of suicidal acts, and represent an escalation of suicidal intent. According to this view, NSSI represents a "gateway", tending to precede suicidal ideation or lethal intent [26].

Common variable theory

Sometimes, a common variable may account for the co-occurrence of suicide attempts and NSSI in the same person. NSSI almost certainly increases the risk for suicidal behaviour, but both may emerge from a psychiatric disorder such as a personality or major affective disorder. This possibility is consistent with evidence that both NSSI and suicide are associated with psychological distress, depression, low self-esteem and lack of social support [26]. Finally, it may be that all of the three preceding theories may contribute to the occurrence of NSSI [26]. In general, NSSI (like suicide) is associated with a broad range of psychiatric disorders, and sometimes with multiple diagnoses, particularly major affective, personality and substance abuse disorders [1 3].

Treatment

Pharmacological treatments

Many psychopharmacological agents have been tried in

TABLE I.
Comparison of suicide attempts and non-suicidal self-injuries (NSSI).

Factors	Suicide attempts	NSSI
Diagnostic criteria	Require lethal intent	Require lack of lethal intent
Median onset age	Mid-adolescence	Late latency, early adolescence
Prevalence		
Adults:		
General population	< 1%; lifetime; 0.10%-0.20%/year	2%-6% lifetime
Psychiatric disorders	20%-30% lifetime, 2%-4%/year	15%-25% lifetime
Adolescents:		
General population	< 1% lifetime	15%-20% total
Psychiatric disorders	10%-20% total, 1%-2%/year	35%-55% total
Sex risk-ratio	Female > male (attempts); Male ≥ female (4-fold; suicide)	Similar in females and males
Frequency per person	Very few lifetime acts	Many lifetime acts (≥50% of cases have ≥5 episodes; About 1% have hundreds)
Adverse medical outcome	Variable, uncommon if survived	Variable severity
Fatality risk		
General population	1/20-30 attempts (geriatric risk greater)	Rare
Psychiatric disorders	1/5-10 attempts	Very uncommon
Associated disorders	Mood disorders, borderline & other personality disorders	Mood, personality, obsessive-compulsive psychotic disorders
Associated emotional states	Severe depression, despair, anger, agitation, impulsivity	Dysphoria, guilt, depression typically less severe than with suicide attempt
Methods	Poisoning, firearms, jumping	Cutting, burning (especially females); hitting, burning (especially males); sometimes multiple
Psychosocial factors		
Predictors	Major affective disorder, depression, hopelessness, post-traumatic stress disorder, prior acts	Negative temperament, poor adaptive skills, pessimism, social isolation or contagion
Correlates	Hopelessness, overwhelming psychic pain	Depression, anhedonia, anxiety, frustration, anger
Motivations	Escape	Temporary relief of psychic distress, punishment
Consequences	May worsen guilt and depression	Rapid relief of psychic distress (encouraging more acts)
Biological factors	Uncertain	Uncertain

Data are based on references cited in the text.

the treatment of NSSI. Most of the relevant studies are anecdotal case reports or series, and well-designed, large, long-term, controlled trials are lacking [1 31 43]. Agents employed have included antidepressants of various types, older and modern antipsychotics including clozapine, mood-stabilisers including anticonvulsants and lithium, anxiolytics and the opioid antagonist naltrexone. None has yet emerged as clearly superior or as a treatment of first-choice.

Psychosocial treatments

Many forms of formal psychotherapies have been applied to the treatment of NSSI, largely in parallel with studies of suicidal behaviour, including cognitive-behavioural techniques (CBT) and dialectic-behavioural treatment (BDT). These approaches are reviewed critically and in detail elsewhere [1 31 44]. There has been particular interest in the use of DBT owing to evidence of superiority to dynamic, insight-oriented psychotherapy and to treatment by suicide experts, at least for reducing risk of suicide attempts in patients with borderline personality disorder [45]. Other interventions with promising beneficial effect in NSSI include psychoeducation, family therapy and physical exercise [1]. Treatment studies have rarely been continued for more than one year, and the long-term outcome and prognosis

in NSSI remains remarkably little studied. Such studies need to differentiate NSSI from suicidal behaviours, to consider specific clinical and age-groups and to pursue outcomes for at least several years.

Conclusions

The relationship between NSSI and suicide attempts is somewhat complex but important to understand. Historically, there has been a lack of clear distinction of self-injurious acts occurring without apparent suicidal or lethal intent (NSSI), and suicidal acts in which there is some degree of intent to die. NSSI and suicide attempts differ in important ways. By definition, NSSI is performed primarily to reduce overwhelming negative emotions without an explicit or conscious intent to die. NSSI is also performed more frequently and with less medical severity compared to suicide attempts, and has a different pattern of psychosocial correlates (Table I). These include, notably, apparent ability of NSSI acts to provide immediate, short-term relief of psychic distress that is not typical of suicide attempts; indeed, this beneficial effect probably reinforces and encourages more self-injurious acts. NSSI and suicide attempts can occur in the same person at different times, and both share causal or contributing factors, including negative self-concepts, depression, guilt, and behavioural disinhibition. Thus, NSSI is appropriately viewed clinically as behaviour that is distinct from suicide attempts in terms of its clinical meaning, to the extent that lethal intent is lacking, but as an important risk factor for suicide that requires ongoing assessment of suicidal intent. There is a pressing need for more, better-designed and longer treatment trials for NSSI.

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Hoarding disorder: a new obsessive-compulsive related disorder in DSM-5

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Summary

Obsessive-compulsive disorder (OCD) and related disorders have been the subject of significant revisions in the fifth edition of the Diagnostic and Statistical Manual (DSM-5). One of these major changes has been the removal of OCD from the 'Anxiety Disorders' section and its instalment in a new and distinct Obsessive-Compulsive and Related Disorders (OCRDs) chapter. However, it is the instatement of hoarding disorder (HD) as a new OCRD that marks the most significant change. Previously considered a symptom of OCPD, and subsequently linked to OCD, it is now acknowledged that hoarding can emerge independently from any alternative condition. The present paper provides an updated review of recent investigations supporting the status of HD as an independent nosological entity. Specifically, we will present the new DSM-5 diagnostic criteria and examine the literature pertaining to the psychopathological and phenomenological aspects of the disorder, with particular attention to practical strategies that can help clinicians to recognise and differentiate HD from OCD. Finally, the available assessment and treatment strategies for HD are summarised.

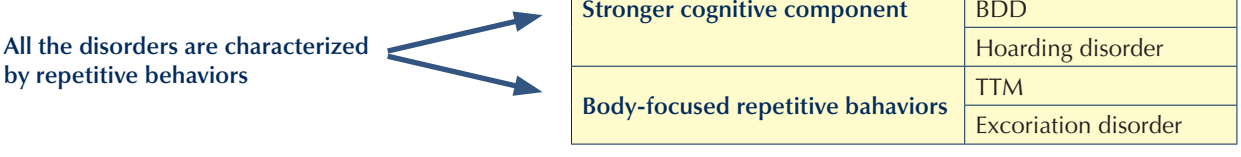
Key words

Hoarding disorder • Obsessive-compulsive and related disorders • Psychopathology • Epidemiology

Introduction

Obsessive-compulsive disorder (OCD) has been the subject of significant revisions in the fifth edition of the *Diagnostic and Statistical Manual* (DSM-5). One of these major changes has been the removal of OCD from the 'Anxiety Disorders' section and its inclusion in a new and distinct category of *Obsessive-Compulsive and Related Disorders* (OCRDs) – a classification which now also includes body dysmorphic disorder (BDD) (previously in the chapter of Somatoform Disorder), trichotillomania (previously classed among the Impulse Control Disorders and now termed hair-pulling disorder), and two *new* disorders, excoriation (skin-picking) disorder and hoarding disorder (HD), alongside the residual categories of substance/medication-induced OCRDs, OCRDs due to another medical condition, and other specified OCRDs. All disorders included in this chapter share similarities with OCD, although some appear to have a stronger cognitive component – and thus are closer to OCD – while others mainly consist of body-focused repetitive behaviours (Figure 1). The 11th revision of the *International Classification of Diseases* (ICD-11) will likely contain a similar OCDRDs chapter, including HD.

While the introduction of two new disorders in the psychiatric nomenclature is independently noteworthy, it



OCD: obsessive-compulsive disorder; BDD: body dysmorphic disorder; TTM: trichotillomania (hair-pulling disorder).

FIGURE 1.
Obsessive-compulsive and related disorders (OCRDs).

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is the instatement of HD that marks, perhaps, the most significant change. Previously classified as a symptom of obsessive-compulsive personality disorder (OCPD) in DSM-IV, and only indirectly linked to OCD, it has only been recently acknowledged that hoarding can emerge independent of any alternative condition. Its formalisation as an independent psychiatric condition in DSM-5 and ICD-11 therefore reflects a marked change, and one that has been precipitated over the last decade by an exponential growth in the number and quality of investigations concerned with this behaviour [1].

The aim of the present paper is to provide an updated review of the HD literature. Specifically, we will present the new DSM-5 diagnostic criteria and examine the work pertaining to the psychopathological and phenomenological aspects of the disorder, with particular attention paid to those aspects that can help clinicians to recognise and differentiate HD from OCD. In addition, we will also highlight the psychopathological and clinical features that may help distinguishing HD and OCD when both conditions coexist. In the final sections, we will summarise the available evaluation and intervention strategies for HD.

Definition and diagnostic criteria of HD

Like most human behaviours, saving and collecting possessions may be viewed along a continuum, with one end representing common and adaptive behaviours (accumulating and storing resources, collecting), which are widespread phenomena in the general population and are evident even during infancy and the other end pertaining to behaviours that are excessive or pathological (excessive acquisition of possessions and failure to discard them). The term 'hoarding,' which first appeared in a paper by Bolman and Katz [2], refers to the latter extreme of this continuum, though it has been noted that hoarding behaviour may not always be pathological [3]. Modern recognition of hoarding as a disorder, and the formal definition of this disorder's pathological features, began with Frost and colleagues several decades later [4 5]. These authors conceived 'compulsive hoarding' (a term no longer in use) as excessive collecting and an extreme inability to discard worthless objects, and proposed an operational definition that would eventually form the basis of the DSM-5 criteria for HD. These early criteria defined 'compulsive hoarding' as: 1. the acquisition of and failure to discard a large number of possessions that seem to be useless or of limited value; 2. living spaces sufficiently cluttered so as to preclude activities for which those spaces were designed; and 3. significant distress or impairment in functioning caused by the hoarding [5].

Despite the significant burden caused by hoarding behaviours, classification systems did not characterise this activity as an independent clinical entity until the publication of DSM-5. Prior to this, hoarding only appeared in DSM-IV-TR where it was classed as one of the eight symptoms/criteria for the diagnosis of obsessive-compulsive personality disorder (OCPD) (*is unable to discard worn-out or worthless objects even when they have no sentimental value*). However, in the text accompanying these criteria, it was explicitly mentioned that *a diagnosis of OCD should be considered* – instead, or in addition to that, of OCPD – particularly *when hoarding is extreme (e.g., accumulated stacks of worthless objects present a fire hazard and make it difficult for others to walk through the house)*. While DSM-IV-TR did not mention hoarding directly as a symptom of OCD, the manual suggested a link between such symptoms and OCD [1].

In accordance with this nosological approach in DSM-IV-TR, hoarding has been long considered a behaviour/symptom dimension of OCD, a view that has been supported by factor analytic studies highlighting the prominence of hoarding as a distinct symptom dimension of OCD (e.g., [6 7]). The inclusion of hoarding items on measures and scales specific to OCD, such as the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) or the Obsessive-Compulsive Inventory-Revised (OCI-R), also served to reinforce an association. For example, the Y-BOCS symptom checklist includes an entry for hoarding/saving obsessions (*worries about throwing away seemingly unimportant things that you might need in the future, urges to pick up and collect useless things*) and hoarding/collecting compulsions (*saving old newspapers, notes, cans, paper towels, wrappers, and empty bottles for fear that if you throw them away you may one day need them; picking up useless objects from the street or from the garbage can*).

However, alongside and in contrast to these developments, several studies began to emerge providing evidence that hoarding may represent a clinical entity distinct from OCD [1 8-12]. First, several studies emerged (see Table I) noting that hoarding, as an abnormal or excessive behaviour, can occur in the context of a variety of neurological and psychiatric conditions beyond OCD, including dementia, cerebral lesions, schizophrenia, major depressive disorder, or generalised anxiety disorder [13 20]. Then came crucial clinical studies that noted that the majority of individuals presenting with prominent hoarding behaviours were not presenting with other obsessive-compulsive symptoms/dimensions and, ultimately, could not be found to fulfil the criteria for OCD. For example, Frost et al. [21] found that among 217 individuals with pathological hoarding, only 18% had a comorbid OCD diagnosis, with comorbidity rates for other, ostensibly unrelated disorders ranged considerably higher (e.g. 51% for major depressive disorder, 24% for social phobia, 24% for generalized anxiety

TABLE I.
Prevalence of hoarding behaviours in illnesses other than OCD.

Illness	Prevalence of hoarding behaviours	Authors
Moderate to severe Dementia	22.6% 15-25%	Hwang et al., 1998 [13] Marx et al., 2003 [14]
Prader-Willi syndrome Velocardiofacial syndrome	37-58% 11%	Dykens et al., 1996 [15] Gothelf et al., 2004 [16]
Schizophrenia	5% 40%	Stein et al., 1997 [17] Wustmann et al., 2005 [18]
Social Phobia	15%	Tolin et al., 2011 [19]
GAD	29%	Tolin et al., 2011 [19]
Compulsive buying	62%	Mueller et al., 2009 [20]

disorder). Additional findings of interest concerning the distinction of hoarding and OCD have included: 1) insights on the phenomenological differences between hoarding and 'classical' obsessive-compulsive symptoms [9-11], 2) a lack of or modest correlation between hoarding and other OCD dimensions [9 22], 3) distinctions in the neural bases for hoarding and OCD [23 25], and 4) differences between OCD and hoarding patients with regard to symptomatology, clinical course and anti-obsessional treatment response [26-30]. Taken together, this body of evidence strongly supported a formal move to distinguish hoarding from OCD, with the introduction of HD as a distinct clinical entity in DSM-5. The decision to title this entity 'HD', rather than 'compulsive hoarding' as was initially suggested in the literature was due to further underline its autonomy from OCD and to avoid confusion between the two disorders. Still, despite these distinctions, HD has retained some link to OCD, with both conditions being contained in the DSM's OCRDs chapter.

The DSM-5 diagnostic criteria for HD are reproduced in Table II. As shown there, the cardinal feature of HD is a persistent difficulty discarding or parting with possessions (criterion A). Though very similar to Frost's original criteria, the DSM version does not specify that items must be 'useless' or of 'limited value', with research suggesting that the most commonly saved items are useful items such as newspapers, books, bags, clothing and the like [9]. In the context of HD, difficulties discarding such items must be due to the perceived usefulness or aesthetic value of the items (intrinsic value – items are valuable or may become in handy in the future), a strong sentimental attachment to the possessions (emotional value), the wish to avoid creating waste, or a combination of these factors [31].

Also essential for the diagnosis is that the person feels distressed when confronted with the idea of discarding or parting with the possessions (criterion B). As detailed in subsequent sections, this criterion is particularly essential for differentiating OCD-related hoarding (hoarding secondary to obsessions in OCD), where attachment to the possessions is not typically present, from true HD.

The excessive collecting results in the accumulation of possessions that congest and clutter active living areas and substantially compromises their intended use (criterion C). Consequences of severe hoarding may be, for example, the inability to cook in the kitchen, sleep in a proper and clean bed, or even move from one room to the other; severe HD poses a broad range of health risks both for patients and their family members, including risk of fire, falling, poor sanitation and even being trapped by a 'clutter avalanche' [31-33].

The hoarding causes significant distress or impairment in social, occupational, or other areas of functioning (criterion D). Quality of life of patients and family members is severely affected, and family relationships are often considerably strained [33-35]. Often, the person with HD does not fully recognise the consequences of their hoarding behaviours, and another family member is the help seeker who asks for the intervention of a mental health provider.

A proper diagnosis of HD requires a differential diagnosis; cluttered living spaces should not assumed to be a manifestation of HD, as they may result from multiple conditions (see Table I) such as brain injury, cerebrovascular disease, Prader-Willi syndrome (see criterion E), or be the product (or secondary manifestation) of symptoms of other mental disorders such as typical obsessive-compulsive symptoms in OCD, decreased energy in major depressive disorder, delusions in schizophrenia or another psychotic disorder, cognitive deficit in major neurocognitive disorders, or restricted interests in autism spectrum disorder (criterion F). HD should also be differentiated from normative collecting. Table III (from Nordsletten et al. [36] &

TABLE II.
DSM-5 diagnostic criteria for HD.

A.	Persistent difficulty discarding or parting with possessions, regardless of their actual value
B.	This difficulty is due to both a perceived need to save the items and distress at the thought of discarding them
C.	The difficulty in discarding possessions results in the accumulation of possessions that congest and clutter active living areas and substantially compromises their intended use; if living areas are uncluttered, it is only because of the interventions
D.	of third parties (e.g., family members, cleaners, or authorities)
E.	The hoarding causes clinically significant distress or impairment in social, occupational, or other important areas
F.	of functioning (including maintaining a safe environment for self and others)
G.	The hoarding is not attributable to another medical condition (e.g., brain injury, cerebrovascular disease, or the Prader-Willi syndrome)
H.	The hoarding is not better explained by the symptoms of another mental disorder (e.g., obsessive in obsessive-compulsive disorder, decreased energy in major depressive disorder, delusions in schizophrenia or another psychotic disorder, cognitive deficit in major neurocognitive disorder, or restricted interests in autism spectrum disorder)

Specify if:
With excessive acquisition: if difficulty discarding possessions is accompanied by excessive acquisition of items that are not needed or for which there is no available space.

Specify:
With good or fair insight: the individual recognizes that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are problematic.
With poor insight: the individual is mostly convinced that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are not problematic despite evidence to the contrary.
With absent insight/delusional beliefs: the individual is completely convinced that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are not problematic despite evidence to the contrary.

Mataix-Cols [31]) provides some clinical criteria that might be helpful in distinguishing common and non-pathological collecting behaviour from HD.
Sometimes, a diagnosis of HD can also be suggested in cases of severe domestic squalor, which tends to be more frequent in old people. Squalor is frequently associated to cases of object acquisition/accumulation due to 'organic' pathology. Cases of 'organic' hoarding may be differentiated from HD on the basis of some phenomenological differences that are summarised in Table IV (from Snowdon et al. [37]).
DSM-5 considers two specifiers for HD: presence of excessive acquisition and degree of insight (Table II). The first applies when 'the difficulty discarding possessions is accompanied by excessive acquisition of items that are not needed or for which there is no available space'; the vast majority of patients with HD present with excessive acquisition [38 39] and this subtype has been associated with more severe hoarding, earlier onset and higher comorbidity rates [38]. Failure to address excessive acquisition in treatment has been linked to treatment failure [37]. An insight specifier is also provided, which may be used to characterise an HD patient's level of insight into their behaviour and its consequences. This insight specifier is clinically relevant because treatment strategies depend on whether or not (and to which degree) the individual recognises that hoarding-related beliefs and behaviours (pertaining to difficulty discarding items, clutter, or excessive acquisition) are problematic: in cases of poor insight, for example, motivational interviewing techniques may be recommended before cognitive-behavioural therapy [40].

HD and OCD

As noted in prior sections, hoarding has traditionally been considered a symptom or symptom dimension of OCD. This association is not without reason, as a proportion of OCD patients (ranging from 18 to 40%) have been found to display hoarding symptoms [41-44]. However, while present in a proportion of cases, only a minority of these OCD patients (approximately 5%) presents this dimension as the most prominent clinical manifestation.
Several phenomenological differences exist between hoarding symptoms that emerge as part of OCD and hoarding that fulfils the criteria for HD. For example: 1) HD-related thoughts are, in contrast to traditional obsessions, not usually experienced as intrusive, repetitive, and distressing; additionally, HD-related thoughts are associated with pleasure and reward in most cases, and are frequently unrelated to other prototypical OCD themes (while compulsions are usually linked to obsessions in

TABLE III.
Differences between normative collecting and HD [31 36].

	Normative collecting	HD
Object content	Very focused; objects are bound by a cohesive theme, with a narrow range of object categories	Unfocused; objects lack a cohesive theme, and the accumulation contains a large number of different object categories
Acquisition process	Structured; planning, searching for items, and organising the collected items	Unstructured; lack of advance planning, focused searching and organisation
Excessive acquisition	Possible, but less common; primarily bought items acquired	Very common; estimates consistently > 80%, with both free and bought items acquired
Level of organization	High; rooms are functional, and collected items are arranged, stored, or displayed in an orderly fashion	Low; the functionality of rooms is compromised by the presence of disorganised clutter
Presence of distress	Rare; for the majority of collectors, the activity is pleasurable, although for a minority, collecting may result in distress due to factors other than clutter (e.g. finances)	Required for the diagnosis; distress is often a consequence of the presence of excessive clutter, forced discarding, or inability to acquire
Social impairment	Minimal; collectors have high rates of marriage, and the majority report forming and engaging in social relationships as part of their collecting behaviour	Often severe; HD is consistently associated with low rates of marriage and with high rates of relationship conflict and social withdrawal
Occupational interference	Rare; scores on objective measures indicate that collectors do not have clinically significant impairment at work	Common; occupational impairment increases with hoarding severity; high levels of work-based impairment have been reported

some ways); 2) in HD, symptoms are perceived as egosyntonic, unlike hoarding thoughts in OCD, which are generally egodystonic; 3) in HD, distress comes from clutter, while it comes from intrusiveness in traditional OCD; and 4) in traditional OCD, the thoughts lead to urges to get rid of them and/or perform a ritual to relieve them, while this is not common in HD [9 31 45 46]. Additionally, the drive for keeping items is different in HD and in OCD-related hoarding; in HD, the hoarding of items is the result of 1) a fear that the items will be needed in the future (intrinsic value) or 2) a strong emotional attachment to the possessions. Crucially, individuals with HD have a genuine desire to possess their items. Such characteristics stand in strong contrast to the views and experiences of OCD individuals who engage in hoarding behaviour (Table V).

Hoarding should be viewed as a symptom of OCD only when it is clearly secondary to typical obsessions, and the relationship between these obsessional thoughts and the resulting behaviour (i.e., hoarding) is the same as that between traditional obsessions and compulsions. To fit with this definition, the hoarding should either relieve obsessional doubts (like a checking compulsion; hoarding as preventive of something bad happening); prevent harm from aggressive obsessions (e.g., *something bad will happen if things get thrown away*) or contamination fears (like preventive or washing compulsions; e.g., *I will contaminate the others because I spread contamination through items*); or relieve feelings of incompleteness or not-just-right experiences (like repetition or symmetry compulsions). Other examples of hoarding resulting from prototypical obsessive-compulsive symptoms include the need to discard items in certain 'lucky' numbers, or the need to perform mental compulsions when discarding any item, so that hoarding appears as an avoidant behaviour [9] (see Pertusa et al. [46] for a case series of OCD-related hoarding). In all these cases, hoarding should be conceptualised as a compulsion, and not as an independent entity of HD.

It has been suggested that hoarding and OCD might coexist in the same patient and yet be completely independent conditions (comorbid conditions). In such cases, careful differential diagnoses will be required to establish which behaviours stem from HD, and which are secondary to classical, prototypical obsessive-compulsive symptoms [9]. Making a diagnosis of OCD and/or HD may be confusing for many clinicians. Consideration of a few key clinical questions may be helpful for this differential process: 1) is the hoarding behaviour driven mainly by prototypical obsessions or is it the result of persistent avoidance of onerous compulsions (more likely in OCD-related hoarding)?; 2) is the hoarding behaviour generally unwanted and highly distressing for the patient (more likely in OCD-related hoarding)?; 3) does

TABLE IV.
Phenomenological differences between accumulating behaviours due to macroscopic brain damage in brain injured or demented patients and hoarding in HD [37].

	"Organic" object acquisition/accumulation	HD
Onset	Generally sudden in cases of brain damage. Can be more insidious if secondary to a dementing process	Insidious. Usually starts in childhood/ adolescence and has a long natural history
Ability to discard hoarded items	Variable (some are able to discard their possessions easily or do not care if others discard them, whereas others are very reluctant)	Inability to discard hoarded items is a core feature of HD
Nature of acquiring behaviour	Generally indiscriminate but can be more selective (acquisition of specific items – e.g. umbrellas – or according to their shape/colour) in some cases	Items are always acquire/hoarded according to their perceived intrinsic, practical, or emotional value, but can be more indiscriminate in some cases
Utility of hoarding behaviour	Often purposeless (individuals display little or no interest in the accumulated items) and items seldom used	More purposeful (items are hoarded for specific emotional or practical reasons), although items often not used
Hoarded items	Any item, including rotten food	Any items, though hoarding of rotten food is rare
Squalid living conditions and/or self-neglect	Frequent (especially in cases of dementia)	Thought to be relatively uncommon although more research is needed
Associated features	Severe personality changes as well as behaviours commonly attributable to brain dysfunction such as gambling, inappropriate sexual behaviour, excessive shopping leading to financial difficulties, theft, stereotypes, tics, and self-injurious behaviours	No severe personality changes or other behaviours clearly attributable to brain dysfunction. Excessive acquisition and shopping and stealing can be present
Cognitive processes and motivations for hoarding	Hoarding apparently devoid of identifiable cognitive and emotional processes, although more research is needed	a) information processing deficits: decision making, categorisation, organization, and memory difficulties; b) emotional attachment to possessions; c) behavioural avoidance; d) erroneous beliefs about possessions
Insight and help seeking behaviour	Poor or absent insight. Patients seldom seek help	Insight ranges from good to poor or absent. Initially, hoarding behaviour can be ego-syntonic; it becomes increasingly distressing as clutter increases. Help seeking probably related to degree of insight
Prevalence	Unknown (< 1%)	Approximately 2-5%
Familial	Unknown but anecdotal reports of relatives independently living in squalor have been reported	Yes. Hoarding tends to run in families and appears to be moderately heritable

the individual show interest in the majority of the hoarded items (more likely in HD)? 4) is excessive acquisition present (more likely in HD)? [1]. The *Structured Interview for Hoarding Disorder* (SIHD) [39 47] provides a specific appendix aimed at assisting the clinician in assessing whether the hoarding behaviour is better conceptualised as a symptom of OCD.

HD: prevalence, aetiological factors and clinical characteristics

Prevalence estimates of hoarding behaviour are few in number and have often provided conflicting estimates. This is due, at least in part, to the only recent formalisation of diagnostic criteria for HD. Prior to their introduc-

TABLE V.
Hoarding characteristics in patients with HD *vs* OCD-related (or secondary) hoarding [9-11 45].

	HD	Hoarding as a dimension of OCD
Relationship between hoarding and OC symptoms	Hoarding NOT related to obsessions/ compulsions	Hoarding behaviour is driven mainly by prototypical obsessions or is the result of persistent avoidance of onerous compulsions[a]
Checking behaviour associated with hoarding	Rare and mild	Frequent and severe
Obsessions related to hoarding (i.e. catastrophic consequence or magical thinking)	No	Yes
Mental compulsions related to hoarding (e.g. need to memorise and recall discarded items)	No	Yes
Egosyntonic/egodystonic	Usually egosyntonic: hoarding thoughts are associated with pleasant feelings of safety	Usually egodystonic: intrusive or unwanted, repetitive thoughts
Presence of OC symptoms other than hoarding	No	Yes
Distress	Comes from clutter (product of behaviour)	Comes from intrusiveness
Main reason for hoarding	Intrinsic and/or sentimental value	Other obsessional themes
Type of hoarding		
Common items[b]	Yes	Yes
Bizarre items[c]	No	Yes
Excessive acquisition	Usually present	Usually not present
Age at onset of clutter problem (years)	Early 30s	Mid 20s
Insight	Poor or absent insight frequent	Generally good insight, although poor insight may be present
Course of hoarding behaviour	Hoarding tend to increase in severity as the person ages	Hoarding does not increase in severity as the person ages (usually)
Global severity/interference	Usually moderate	Usually severe

[a] Fear of catastrophic consequence, need for symmetry/order, need to perform checking ritual because of the fear of losing an important item, etc.
[b] Old clothes, magazines, CDs/videotapes, letters, pens, old notes, bills and newspapers, etc.
[c] Faeces, urines, nails, hair, used diapers, and rotten food, etc.

tion, studies evaluating prevalence used their own definitions of clinically meaningful hoarding behaviour and identified members of populations who fulfil these definitions. Indeed, at present, only one study has evaluated prevalence using the DSM-5 criteria for HD, reporting a weighted prevalence of 1.5% [48]. Other studies, using less restrictive characterisations of hoarding, have generally reported higher rates. For example, Samuels et al. [49] analysed data from the *Hopkins Epidemiology of Personality Disorder Study* (N = 742) and estimated the lifetime prevalence of pathological hoarding, measured by means of the hoarding criterion for OCPD, at nearly 4% of the population. In a sample of 5022 twins, the point prevalence of severe hoarding – measured by the self-reported version of the *Hoarding Rating Scale* – was estimated to be lower, 2.3% [50]. Using the same scale, Ivanov et al. [51] found clinically-significant hoarding in 2% of adolescent twins. Timpano et al. [52] found a higher prevalence rate (5.8%) in a representative sample of the German population using the *Hoarding Rating Scale*. Mueller et al. [20] found again a point prevalence of 4.6% in a representative sample of 2307 subjects using the *Savings Inventory-Revised*. Meanwhile, in Italy, a recent set of studies reported point prevalence estimates of self-reported hoarding behaviour (as-

sessed by the *Saving Inventory-Revised*) of 3.7% and 6% in two non-clinical samples [53]. Given this array of findings, and in the absence of additional work using the DSM-5 definition of hoarding, the true prevalence of HD remains unclear. Further studies will be necessary to establish the proportion of the population impacted by this condition, and whether these proportions differ by key demographic factors (e.g., age, gender, ethnicity).

With regards to aetiology, the causes of HD are still largely unknown. Twin studies suggest that a predisposition to HD is genetically transmitted, with approximately 50% of the variance in hoarding behaviours attributable to genetic factors and the remaining variation being attributable to non-shared environment [50]. Candidate genes have yet to be consistently identified for this disorder [54]. While associations have been found between traumatic life events and hoarding symptoms and severity – retrospective studies have found, for instance, that subjects with HD have a greater number of life events – prospective studies are lacking and results remain unreliable [27 30 55]. According to the cognitive-behavioural model of HD, three primary factors contribute to the emergence of hoarding behaviour: 1) beliefs about and emotional attachment to possessions, 2) avoidance behaviours that develop as a result of the emotional distress associated with discarding possessions, and 3) information-processing deficits in the areas of attention, categorisation, memory and decision making [5 56 57]. It is possible that several genetic and psychological vulnerability factors may interact with stressors in order to determine who will develop (and when) hoarding symptoms. However, further research will be needed to untangle such predisposing, contributing and maintaining factors.

Clinical characteristics of HD, such as age at onset or course of the hoarding symptoms, have primarily been derived from studies that investigated hoarding with criteria that are not those of DSM-5. Notwithstanding such limitations, the available literature suggests that hoarding behaviours often begin early in life and tend to increase in severity as the person ages [31]. The threshold for the diagnosis (interference with the person's everyday functioning) is generally reached by the mid-20s, with symptoms continuing to worsen thereafter in the majority of individuals [27 30 51]. Comorbidity is common, with HD clinical samples often presenting with major depressive disorder, anxiety disorders, or attention deficit-hyperactivity disorder [21 39].

The burden of HD often extends beyond the affected individual, and is shared by those around them including family, friends and community members [21 34]. In a recent study, for example, the level of carer burden experienced by HD relatives was found to be comparable to or greater than that reported by relatives of individuals with dementia. Perceived level of squalor, co-habitation with the HD individual and increasing age of the HD individual were all significant predictors of carer burden and functional impairment in relatives [34].

Evaluation of HD

Hoarding symptoms often need to be specifically asked about, as many patients do not spontaneously volunteer this information. Even patients with good insight often underestimate the extent of their hoarding and the consequences of the disorder. The use of some simple screening questions, such as 'are the rooms of your home so full of items that it is hard for you to use these rooms normally?', may initiate a fruitful dialogue and can rapidly lead to the diagnosis.

A formal HD diagnosis requires an interview with a trained assessor, ideally in the person's home environment. The SIHD [39 47] is a freely available, validated, semi-structured instrument that has been designed to assist clinicians with the nuanced evaluation of this disorder. The content of this interview maps directly onto the DSM-5 criteria for HD, with questions relating to each diagnostic criterion and specifiers. Its suitability for establishing the HD diagnosis has been demonstrated in several studies, including the *London Field Trial for Hoarding Disorder*, which showed that diagnoses determined using the instrument showed an excellent balance of sensitivity (0.98) and specificity (1.0) [39].

Because the diagnosis of HD requires the presence of obstructive clutter (Criterion C), diagnostic assessments (such as the SIHD) are ideally done in the sufferer's home environment. This approach enables the clinician to tangibly evaluate the scale of the clutter, assess the extent of the resulting obstruction/impairment, and determine the presence of health and safety risks (e.g., fire hazards, infestations and/or unsanitary living conditions) [35 37]. To assist with this process, the SIHD also contains a risk assessment module.

When in-home assessments are not possible, clinicians can use photographs to assess the extent of clutter[58]. These photographs can be used in combination with the *Clutter Image Rating* (CIR) [59], which consists of a series of photographs depicting increasingly obstructive levels of clutter across the bedroom, kitchen, and living room.

When a patient with HD shows limited or absent insight into their hoarding activity, a situation that may arise in a substantial proportion of hoarding cases, a multiple-informant approach (e.g., seeking both patient reports and information available from third parties) may be helpful [60]. Given that much of this population does not recognise their problem, clinicians may find that few of their hoarding patients are voluntarily presenting for assessment or treatment. Accordingly, during the assessment process,

clinicians should be aware that conflicts may arise between the patient's account of their behaviour and the portrait provided by third parties (e.g., patient records, social service reports, consultation with family members). Discrepancies should be tactfully addressed and clarification requested from all relevant sources. Should discrepancies persist, clinicians will need to exercise their clinical judgment in making a diagnostic determination.

Treatment

Traditionally, hoarding has been treated using approaches designed for OCD, with a focus on serotonergic compounds or cognitive-behavioural therapies (mainly exposure and response prevention). This clinical approach, which is the evidence-based treatment for OCD, has failed to produce satisfactory results in HD. A recent meta-analysis confirmed that patients with OCD and hoarding symptoms are less likely to respond to traditional OCD treatments, this finding being consistent across treatment modalities [61].

In the case of secondary hoarding (i.e., hoarding symptoms in the context of OCD), treatment protocols indicated for OCD should be applied. It may be reasonable to assume that, in these cases, response will be similar to that achieved among OCD cases without hoarding symptoms/behaviours, though this has not been formally tested. Previous studies conducted in the context of OCD likely contained a mix of HD cases and of OCD-related hoarding cases, hence precluding firm conclusions in this regard.

Conversely, when hoarding is conceptualised as an independent or comorbid disorder (e.g., diagnosis of HD and OCD) specific treatment strategies for HD should be applied. Tailored cognitive behavioural therapy for HD, including education and case formulation, motivational interviewing, skills training for organising and problem solving, direct exposure to non-acquiring and discarding, and cognitive therapy, has been found to be effective for hoarders [40]. Several other specific psychological interventions for HD have been developed, and these treatments may be used when HD is diagnosed. A recent meta-analysis confirmed that CBT is a promising treatment for HD, although there is significant room for improvement [62]. Empowering family members of subjects with HD with specific training programs seems to be an effective add-on treatment as well [63].

Only two studies have specifically investigated the effectiveness of pharmacological treatments in HD. Both studies, one for paroxetine [64] and the other for venlafaxine extended-release [65] were positive; however, both are small, uncontrolled studies and are hampered by methodological limitations (particularly regarding recruitment and assessment methods).

Although the number of studies investigating treatment in the field is growing and results are generally positive and promising, it also has to be acknowledged that effective treatments for HD are still far from satisfactory. Double-blind, psychological and pharmacological placebo-controlled trials are strongly warranted and needed in patients with HD.

Conclusions

The inclusion of the new diagnosis of HD in DSM-5 within the OCRDs chapter will help researchers in studying clinical characteristics of the disorder and implementing effective treatments for those patients. There is, in fact, a strong need at present for finding treatment strategies which are both acceptable by patients and effective in treating the disorder.

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Separation anxiety disorder in the DSM-5 era

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Summary

Separation Anxiety Disorder has been recently classified into the DSM-5 section of Anxiety Disorders, acknowledging its role not only in childhood and adolescence but also across the whole lifespan. In the DSM-IV-TR, in fact, this condition was typically considered to begin in childhood. Clinical data report prevalence rates from 20 to 40%, showing high comorbidity rates with most mental disorders. Epidemiological data highlight that in fact one third of childhood cases persist into adulthood, while the majority of adult cases reports its first onset in adulthood. In all cases, Separation Anxiety Disorder is associated with a severe impact on the overall functioning. Most relevant research in the field is discussed highlighting the need of a paradigm shift in which clinicians are alerted to identify and treat this condition in all age upon the recent DSM-5 reformulation will be highlighted.

Key words

Separation anxiety • Panic disorder • Anxiety disorders • Complicated grief • Post-traumatic stress disorder

Separation anxiety disorder across the DSM-5

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [1] has recently introduced important classification changes, including the introduction of Separation Anxiety Disorder has into the section of Anxiety Disorders. In the DSM-IV-TR [2], unlike other anxiety disorders, Separation Anxiety Disorder was considered a condition typically beginning in childhood that could be diagnosed in adults only "if onset is before 18 years of age". For this reason, although most anxiety disorders typically start in childhood or adolescence, this was the only one placed under the label "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence". Notwithstanding, the DSM-IV-TR did not actually preclude a diagnosis in adulthood, stating that "adults with the disorder are typically over concerned about their offspring and spouses and experience marked discomfort when separated from them", such classification led clinicians to usually overlook this condition in their adult patients [3 4].

By removing the age-of-onset criterion, the DSM-5 acknowledged Separation Anxiety Disorder as a condition that may span the entire life, but also begin at any age, leading to its inclusion among Anxiety Disorders. Despite age of onset before 18 years is not longer needed, the DSM-5 states that it usually begins in childhood and more rarely in adolescence, somehow indicating that first onset in adulthood is uncommon, and that the majority of children with Separation Anxiety Disorder are considered to be free of impairing anxiety over their lifetime. However, it has been shown that more than one third of subjects classified as childhood cases might persist into adulthood [5] and some epidemiological and clinical data have highlighted that the prevalence of Separation Anxiety Disorder might be greater among adults than in children and that the vast majority of persons classified as having adult Separation Anxiety Disorder report first onset in adulthood, with a peak of onset in early 20s [5 6].

The essential feature of Separation Anxiety Disorder is an inappropriate and excessive anxiety concerning separation, actual or imagined, from home or major attachment figures, causing clinically significant distress or impairment in functioning. Symptoms may include recurrent excessive stress when anticipating or experiencing separation from major attachment figures or home, persistent and excessive worry about losing major attachment figures or about potential harm befalling to them. Furthermore, in response to fear of separation from an attachment figure, patients may show excessive worry about experiencing a negative event (e.g., an accident or illness, being lost or kidnapped), refusal to leave home to go to school or to work, fear of being alone or without major attachment figures at home or in other settings; reluctance or refusal to sleep away from home or to go to sleep; repeated nightmares involving the theme of separation; repeated complaints of physical symptoms when separation from major attachment

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figures occurs or is anticipated. Besides deleting the age limitation, the DSM-5 requires that fear, anxiety, or avoidance last 4 weeks or more in children and adolescents, and at least 6 months in adults.

Prior to the introduction of the DSM-5 criteria, the literature in this field investigated adult Separation Anxiety Disorder generally using semi-structured interviews based on existing DSM-IV-TR criteria adapted to adulthood. Specific terms had, in fact, been adopted across different studies. Adult-onset Separation Anxiety Disorder refers, in fact, to an adult Separation Anxiety Disorder diagnosis without a documented history of childhood Separation Anxiety Disorder, whereas childhood-onset adult Separation Anxiety Disorder refers to an adult Separation Anxiety Disorder diagnosis in individuals who have also met the criteria of Separation Anxiety Disorder during childhood.

In adult patients, anxiety might focus on parents, but more often involves intimate partners and children [7 8], with marked discomfort when separating from them [1]. While in children worries usually concern accidents, kidnapping and deaths, adults suffering from Separation Anxiety Disorder may also show difficulties in coping with changes in circumstances, such as moving or getting married [1]. Somatic symptoms that are usually prominent in childhood Separation Anxiety Disorder, such as nausea and stomachaches [2], seem to be less frequent in adults who instead show more cognitive and emotional symptoms [7]. Moreover, as a way to deal with their fears and ensure a contact with attachment figures, adults with Separation Anxiety Disorder might make frequent phone calls, adhere to rigid routines or talk excessively.

Despite most youths suffering from Separation Anxiety Disorder are thought to make a good recovery through puberty and adult life [1], the long-term outcome of childhood Separation Anxiety Disorder is actually not clear. Besides some studies identifying it as either a specific risk factor for adult panic disorder (PD) [9] or a general risk factor for multiple adult mental disorders [10-12], growing clinical and epidemiological data have been showing that Separation Anxiety Disorder may also persist through adulthood. The available epidemiological data, in fact, indicate that the lifetime prevalence of Separation Anxiety Disorder in the general adult population ranges from 4.8 to 6.6% [5 13]. Moreover, despite the assumption that late onset is uncommon, many persons classified as having adult Separation Anxiety Disorder report first onset in adulthood [13 5].

Epidemiological and clinical data

Adult Separation Anxiety Disorder was first explored in clinical settings with prevalence rates ranging approximately between 20 and 40% [14 15]. Manicavasagar et al. [14] showed a prevalence of adult Separation Anxiety Disorder, assessed with the *Adult Separation Anxiety Symptom Questionnaire* (ASA-27), of 46% in patients with PD or generalised anxiety disorder. Consistently, in a large cohort of 508 outpatients with anxiety and mood disorders assessed by means of DSM-IV-TR criteria adapted to adulthood, a prevalence of adult Separation Anxiety Disorder was found to be as high as 42.4%, with about 50% of these latter cases reporting an adulthood onset of the disorder [6]. Silove et al. [15], on a large sample of anxiety patients, reported an estimate prevalence of adult Separation Anxiety Disorder was 23%.

Two recent investigations also provide some epidemiologic data about Separation Anxiety Disorder. The National Comorbidity Survey (NCS-R) [5], carried out on 5692 adults, found Separation Anxiety Disorder to be common in the US, as lifetime prevalence estimates of childhood and adult Separation Anxiety Disorder were 4.1% and 6.6%, respectively. Diagnosis was based on retrospective assessments using a criterion set parallel to that of the DSM-IV-TR [2], "making age-appropriate modifications to the criterion A symptom questions". One third of childhood cases persisted into adulthood, while the majority of adult cases had first onset in adulthood. Moreover, Separation Anxiety Disorder was significantly more common in women than men, in people between 18 and 59 years, and in the never married and previously married (compared to the currently married or cohabiting). More recent data from the World Mental Health Surveys of the World Health Organization (WHO) show lifetime prevalence Separation Anxiety Disorder rates as high as 4.8% across Countries, with almost a half of lifetime onsets occurring after the age of 18 [16]. Controlling for lifetime comorbid disorders, age and country, Separation Anxiety Disorder was significantly associated with being female, having low through high-average education, maladaptive family functioning childhood, other childhood adversities, and a variety of lifetime traumatic events. It is noteworthy that the associations between maladaptive family functioning, childhood adversities and other lifetime traumatic events predicted not only paediatric-onset, but also adult-onset Separation Anxiety Disorder.

Childhood Separation Anxiety Disorder is more common in girls with almost twice as much as the rates reported in boys [16]. Conversely, gender differences appear to be less strong in adult Separation Anxiety Disorder, despite females appear to be more symptomatic than men [5 16 17] and males are more likely to report first onset in adulthood [5]. Clinical studies are in line with these data. When comparing outpatients with anxiety and mood disorders with and without adult Separation Anxiety Disorder, higher

female/male ratios were found in those with than those without adult Separation Anxiety Disorder [6]. In addition, a study on early separation anxiety symptoms of adult patients with Separation Anxiety Disorder found elevated scores only in females [15].

Comorbidities with other mental disorders

Epidemiological investigations show that adult Separation Anxiety Disorder is highly comorbid with other mental disorders and is associated with substantial impairment in role functioning that persists even after controlling for comorbidity [5]. The WHO Mental Health Survey data also revealed significant time-lagged associations between Separation Anxiety Disorder and other disorders, including not only internalising disorders (e.g., major depression, bipolar disorder, specific and social phobias, PD, generalised anxiety disorder and/or post-traumatic stress disorder), but also externalising ones (e.g., ADHD, oppositional defiant disorder, and conduct disorder), supporting the hypothesis that Separation Anxiety Disorder represents a generic risk factor for a range of common mental illnesses. As for clinical samples, growing evidence shows that Separation Anxiety Disorder is common in psychiatric settings. Prevalence estimates ranging from 23% to 65% have, in fact, been reported among patients with mood and anxiety disorders [6 15].

Anxiety disorders

A close relationship between Separation Anxiety Disorder and PD has been consistently found in adult patients [15 18-20]. The relationship between Separation Anxiety Disorder and PD is still debated. Separation sensitivity is considered a dimension of PD and, therefore, it was included among the panic-agoraphobic spectrum symptoms [21 22]. On the other hand, the agoraphobic-like dimension of Separation Anxiety Disorder might enhance the comorbidity between this latter and PD, and raises doubts about its distinctiveness. However, researchers have pointed out the fact that Separation Anxiety Disorder often precedes the onset of other anxiety disorders, and postulated that panic attacks might be secondary to Separation Anxiety Disorder [8 14 23]. A recent meta-analysis [19] found that a childhood diagnosis of Separation Anxiety Disorder significantly increases the risk of PD and other anxiety disorders, confirming that this disorder may represent a vulnerability factor for mental illnesses.

Mood disorders

People with adult Separation Anxiety Disorder show higher levels of depression even without high comorbidity rates with Major Depressive Disorder (MDD) [6 15]. Interestingly, Kossowsky's [19] meta-analysis confirmed that, after adjusting for publication bias, childhood Separation Anxiety Disorder is not associated with adult MDD. On the other hand, some investigations suggested a specific association between bipolar disorders (BD) and Separation Anxiety Disorder [5]. While Separation Anxiety Disorder has been demonstrated to be significantly more frequent in patients with BD type I and PD than those with MDD, a few data indicate a relationship between Separation Anxiety Disorder and mood spectrum symptoms. A strong correlation between Separation Anxiety Disorder symptoms and lifetime mood spectrum symptoms of both polarities was found in patients with complicated grief (CG) and in healthy controls [24]. Similarly, a significant association between lifetime mood symptoms and Separation Anxiety Disorder among subjects with CG, PTSD and PD has been reported [25 26].

Post-Traumatic Stress Disorder (PTSD)

In consideration of the fact that Separation Anxiety Disorder is characterised by intense anxieties and fears concerning separations from or harm to attachment figures, a growing interest has been recently devoted to the pattern of comorbidity involving Separation Anxiety Disorder, PTSD and pathological grief reactions. Some literature data have pointed out the possibility that traumatic events may precipitate Separation Anxiety Disorder in children and adolescents [27 28]. However, only limited data are available about possible associations between traumatic events and adult Separation Anxiety Disorder [5 14 24 25 29 30].

Some evidence suggests that Separation Anxiety Disorder tends to co-occur with PTSD amongst adult populations exposed to traumatic losses and network-related traumas [4 25 29]. Silove et al. [29], in a study exploring trauma-affected Bosnians resettled in Australia, showed that adult Separation Anxiety Disorder was strongly comorbid with PTSD, with almost all individuals with adult Separation Anxiety Disorder having comorbid PTSD, but not with traumatic grief. Moreover, among PTSD dimensions, adult Separation Anxiety Disorder was specifically linked to avoidance and hyperarousal, but not to re-experiencing. This association between Separation Anxiety Disorder and PTSD was also found in the NCS-R study [5] where PTSD was found to be one of the strongest pattern of comorbidity with adult Separation Anxiety Disorder among Axis I disorders. This led the authors to hypothesise that the intense personal insecurity might be the common factor underlying PTSD and adult Separation Anxiety Disorder [29]. In people with adult Separation Anxiety Disorder, this fear for personal safety may drive the need to maintain proximity to attachment figures, while in trauma-affected individuals it may in-

crease the likelihood of experiencing PTSD symptoms. Most recently, an analysis of the cross-national World Mental Health Survey dataset indicated that Separation Anxiety Disorder (assessed across the lifespan) was one of only a few prior disorders statistically associated with subsequent PTSD onset [31], thus preceding and predicting it. Consistently, Tay et al. [30] found that adult Separation Anxiety Disorder symptoms play an important role in mediating the effects of traumatic losses and worry about family in the pathway to PTSD symptoms in 230 refugees from West Papua. In light of these data, the authors proposed an evolutionary model in which the adult Separation Anxiety Disorder and PTSD reactions may represent complementary survival responses designed to protect the individual and close attachments from external threats. In particular, separation anxiety in response to attachment threats could represent a mechanism activating PTSD symptoms through a pathway that may be intensified in the case of repeated threats to close others, as it happens in refugees. In support to this theory, the authors highlighted the evidence that both Separation Anxiety Disorder and PTSD reactions are mediated by neuronal substrates located in the amygdala, which is the brain center responsible for initiating the learned fear response [4 32].

Complicated Grief (CG)

In the past decades, a growing interest has been devoted to the distinction between normal and "pathological" grief processes, particularly complicated and traumatic grief, so that the DSM-5 acknowledged Persistent Complex Bereavement Disorder within the third section of disorders deserving further studies [33-35].

Symptoms of CG may vary and include recurrent and intense pangs of grief, preoccupation with the deceased, recurrent intrusive images of the loved one and a strong desire to join their loved one that can lead to suicidal thoughts and behaviours [34-36]. In the DSM-IV-TR, bereavement was said to be likely present with symptoms of a MDD or PTSD only, this latter in the case of a traumatic death. Nevertheless, increasing data has highlighted grief not to be characterised by prolonged depression but acute and episodic "pangs". Research data, in fact, has suggested its phenomenological closeness to separation anxiety rather than to depressive symptoms.

On the other hand, since Bowlby started his work on attachment [37], separation and loss have always been treated together and attachment theory has offered insight into both separation anxiety and grief. In fact, some studies have reported a link between insecure attachment styles and both complicated grief [38 39] and Separation Anxiety Disorder symptoms [37]. Moreover, it has been proposed that the exposure to a traumatic event, as a loss, may trigger symptoms associated with adult Separation Anxiety Disorder [15 27]; Vanderwerker et al. [40] reported that childhood Separation Anxiety Disorder is linked to a higher risk of developing complicated grief in adulthood.

The first study exploring adult Separation Anxiety Disorder among patients with CG found that these patients showed significantly higher scores on the ASA-27 with respect to healthy control subjects [24]. A later clinical study, aimed at comparing the clinical features of CG with those of patients with PTSD and with PTSD and CG in comorbidity, found that patients with comorbid PTSD and CG reported significantly higher ASA-27 scores compared to patients with one of the two disorders alone [25]. These data corroborated results from Silove et al. [29] who found adult Separation Anxiety Disorder to be associated with PTSD, but not with depression or CG among trauma-affected Bosnians resettled in Australia. Authors argued that the temporal focus of grief and Separation Anxiety Disorder may have accounted for this finding: the former constellation being past oriented, while separation-related anxieties are directed towards the present and future safety of attachments [29]. On the other hand, traumatic loss has been correlated with symptoms of Separation Anxiety Disorder. Boelen et al. [41] reported that prolonged grief disorder, MDD, and adult Separation Anxiety Disorder were better conceptualised as distinct dimensions instead of a unitary dimension of distress. Interestingly, the cause of loss was the single variable that was associated with all three symptom-clusters, with loss due to violent cause giving rise to more severe symptoms. Most recently [20], some of us explored the prevalence and clinical significance of adult Separation Anxiety Disorder in a help-seeking sample of 151 adults with CG. Results showed adult Separation Anxiety Disorder to be highly prevalent among patients with CG and associated with greater symptom severity, greater impairment and more comorbidity with PTSD and PD.

It is noteworthy that recent studies have pointed out that the presence of adult Separation Anxiety Disorder affects treatment outcomes in patients treated with psychotherapy [42 43]. Yet based on these researchers' findings, separation anxiety might be expected to act as a moderator of response to CG treatment in bereaved people.

Perspectives for future research

Developing targeted treatment

While currently included among anxiety disorders, Separation Anxiety Disorder has been considered for a long

time a childhood disorder, such that clinicians are still not fully aware of its prevalence, course and relevance during adulthood. The DSM-5 reformulation of Separation Anxiety Disorder therefore requires a paradigm shift in which clinicians are alerted to identifying and treating the condition in all age groups [44]. However, findings from clinical and epidemiological settings highlight that Separation Anxiety Disorder cause clinically relevant impairment, over and above the effect of concomitant mental disorders. Moreover, growing data are pointing out that the presence of Separation Anxiety Disorder plays a crucial role in moderating treatment outcomes of other comorbid disorders. Kirsten et al. [43] found that patients treated with cognitive-behavioural therapy for PD, social phobia, or generalised anxiety disorder were less likely to show reductions in anxiety and depression when having comorbid Separation Anxiety Disorder. Aaronson et al. [42] found that patients with PD treated with cognitive-behavioural therapy were significantly more likely to show a poor outcome if they had comorbid Separation Anxiety Disorder, even controlling for relevant clinical and demographical variables. More recently, Miniati et al. [45] showed that symptoms of separation anxiety are predictors of poor outcome in adults with PD under psychopharmacological treatment. These findings not only highlight the need of raising clinicians' awareness on Separation Anxiety Disorder, but should also prompt researchers to develop and test targeted treatments for adult patients.

Elucidating developmental pathways of separation anxiety disorder

Notwithstanding the inclusion of Separation Anxiety Disorder among anxiety disorders mostly depended on the acknowledgement of childhood-onset cases persisting through adulthood, growing literature has also shown that Separation Anxiety Disorder might have an onset after puberty and virtually at any age. Therefore, the main challenge about DSM-5 Separation Anxiety Disorder is what may act as a trigger for the adult-onset of the disorder.

While a few studies have elucidated the clinical correlates of adult Separation Anxiety Disorder, no longitudinal studies have been undertaken to accurately evaluate if adult-onset Separation Anxiety Disorder may precede, follow, or come along with other mental disorders. Moreover, limited research has been conducted up to date aiming to investigate whether certain life events may precipitate Separation Anxiety Disorder symptoms during adulthood. However, it is noteworthy that Separation Anxiety Disorder has been found to be highly prevalent among subjects with PTSD and/or CG, and that lifetime traumatic predict adult-onset Separation Anxiety Disorder, suggesting the hypothesis that some sort of life events, such as a personal threat or the loss of a close one, might trigger Separation Anxiety Disorder during adulthood.

The potential value of a neurodevelopmental perspective for understanding aetiological factors in psychopathology has been recently highlighted [46]. Specifically, it has been pointed out that what have been traditionally considered to be distinctive forms of psychopathology may have common features or may represent age-adjusted variations of common underlying dispositions. This might easily fit the debated relationship between early-onset Separation Anxiety Disorder and anxiety disorders of adulthood. On the other hand, integrating such perspective with a vulnerability-stress-disease model, adult-onset Separation Anxiety Disorder may represent the late clinical manifestation of a latent vulnerability, interacting with specific, severe life events. Longitudinal, prospective investigations are warranted to elucidate factors associated with the onset of Separation Anxiety in adulthood with important preventive clinical implications.

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From hysteria to somatic symptom disorders: searching for a common psychopathological ground

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Summary

After decades of manifold contributions aimed at defining hysteria, somatisation and conversion, such syndromes are still neglected and their nosographical definition is debated. The DSM and the ICD have undergone major changes, but their clinical utility with regards to these syndromes is still questionable. On the contrary, the Diagnostic Criteria for Psychosomatic Research represents a useful clinical instrument since it translates psychosocial variables derived from psychosomatic research into operational tools. The present paper offers an overview on the psychopathological description of syndromes such as alexithymia, hypochondriasis, health anxiety, thanatophobia, conversion symptoms, anniversary and reaction which are frequent in clinical practice, but often misdiagnosed due to their absence in the DSM and the ICD. In addition, the influence of culture and cultural changes on the modifications of psychopathological manifestations is described as a further possible source of misdiagnosing and underreporting. New psychopathologies (e.g., multiple chemical sensitivity, orthorexia/vigorexia) that resemble conversion and/or somatisation have been developed, but neither is included in nosography nor taught to clinicians. The aim of the present paper is thus to describe psychopathological manifestations of somatic symptoms and related disorders to help clinicians formulate their diagnosis on the presence of signs and symptoms that can be elicited during a clinical visit, rather than by way of exclusion of other organic or psychiatric disease only.

Key words

Somatic symptom and related disorders • Hysteria • Alexithymia • Hypochondriasis • Health anxiety • Thanatophobia • Conversion symptoms • Anniversary reaction • New psychopathologies

Introduction

Medically unexplained physical symptoms (MUPS) are common and account for up to three-quarters of clinical situations [1]. The most frequent complaints mentioned by patients are pain, fatigue, gastrointestinal and cardiovascular symptoms, and sexual and pseudo-neurological disturbances. Although in most cases these conditions remit spontaneously [2], a small but significant proportion may worsen over time in terms of chronicity, severity of symptoms, impact on functioning, disability, development of medical (iatrogenic) psychiatric comorbidity and lead to excessive/inappropriate use of health care resources [3]. The prevalence of such disorders ranges from 1 to 8% in the general adult population, with a relative risk of 2.7 of 5-year persistence of symptoms and of 1.5 for comorbidity with psychiatric symptoms/disorders. They may account for a 7-fold increase in expenses for healthcare services [4]. The most complex and severe cases are characterised by specific clinical features, such as a high number of somatic symptoms, comorbidity with other psychiatric conditions (i.e., mainly depressive and anxiety disorders), presence of relevant psychosocial risk factors (e.g., history of childhood abuse or violence) [5]. On the other hand, the sometimes cumbersome efforts to establish valuable long-term clinical relationships with these patients have been described as a source for burnout in clinicians [6]. Early identification of predictors for persistent, multiple MUPSs is crucial to help properly patients [5] who otherwise risk to be labeled as "difficult to treat" and hence might develop a chronic course of illness.

From Freud to the DSM-IV: the history of somatisation and conversion disorders

Somatoform disorders (SD) are often thought to be residing in a no-man's land, in the grey area between medicine and psychiatry. Over the years, they have been differently labelled and clinicians and researchers have proposed a wide range of theories for their aetiology, diagnosis and treatment. Briquet [7] was the first who studied a syndrome characterised by multiple somatic symptoms and named it "hysteria" in 1859. Thereafter, Stekel [8] defined hysteria as a bodily disorder arising from the expression of a deep-layered neurosis. Later, Lipowski's [9] definition was: "The

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tendency to experience, conceptualize, and/or communicate psychological states or contents as bodily sensations, functional changes or somatic metaphors". Later, Lipowski placed more emphasis on "somatic distress" which is primarily experienced and communicated by these patients, rather than the "psychological distress". Thus, his definition was revised into: "A tendency to experience and communicate somatic distress and symptoms unaccounted for by pathological findings, to attribute them to physical illness and to seek medical help for them" [10]. This is the basic framework on which the concept of hysteria has evolved over the years.

At the beginning of 1900, Janet and Freud, who had worked with Charcot on hypnosis [11], defined psychic mechanisms in the symptoms of hysteria: dissociation of the consciousness [12] and conversion [13]. Thereafter, Freud and Breuer [14] proposed that mental distress might be "converted" into physical dysfunction. Subsequently, the term "conversion" was used to denote essentially functional neurological disturbances. Although in their initial observations, both Charcot and Janet acknowledged the involvement of body and mind in hysteria, Janet later emphasised that conversion was solely mental in origin, thereby dismissing the role of a physical lesion hypothesised by Charcot [12]. Freud's views have been reflected in the *International Classification of Diseases* (ICD) and in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), in which the role of emotional conflicts – not necessarily accessible for patients – in generating hysteria is highlighted.

Morselli [15], more than a century ago, first described a case of body dysmorphic disorder (BDD), reporting on a young woman who confined herself in her apartment for 5 years, worrying that she would never be loved for being "ugly and ridiculous". This syndrome was classified as "atypical somatoform disorders" in the DSM-III, before the current name of BDD came up in the following edition [16].

The concept of neurasthenia was defined by Beard in 1869, who described it as "a disease of nervous system, without organic lesion, which may attack any or all parts of the nervous system, and characterized by enfeeblement of the nervous force, which may have all degrees of severity" [17]. Neurasthenia was introduced in the DSM-II to increase congruency with the ICD-8, but it was dropped from the DSM-III, although it was maintained in the ICD system as a subtype of neurosis.

The DSM-III derived the concept of "Somatisation disorder" from the criteria of "Briquet's syndrome", as described and operationalised by Perley and Guze [18], who recognised the need to differentiate the "illness characterized by multiple somatic and psychiatric complaints" described by Briquet from the other meanings of the term hysteria, and proposed the eponymous "Briquet's syndrome". In the attempt to avoid overlap with other diagnoses, all psychological symptoms were eliminated from the criteria of the DSM-III revised version [19]. This change, which essentially separated the psychological dimension from the physical one, has obviously drawn some criticisms. Oken [20] stated that the "over reliance on the old biomedical model, rather than the biopsychosocial model by DSM-III downplayed the benefits achieved by its dynamic framework comprising the psychological, biological and social factors".

Compared with DSM-III, the DSM-IV adopted a simpler approach, requiring a combination of pain, gastrointestinal, sexual and pseudo-neurological symptoms for the diagnosis of somatisation disorder (SD) [21]. "Undifferentiated SD" refers to an array of unexplained physical symptoms which did not cross the threshold for full-blown somatisation disorder. "SD not otherwise specified" was kept as a residual category. BDD was added and the definition of conversion disorder modified. The DSM-IV defined "Conversion disorder" as characterized by symptoms affecting voluntary motor and sensory functions, in contrast to the DSM-III definition of any symptom suggestive of a physical disorder [21]. Finally, the criteria for "Pain disorder" were modified to include subtypes associated with: 1. psychological factors; 2. both psychological factors and a general medical condition; 3. a general medical condition.

Current nosography of somatic symptoms

According to the DSM-5, *Somatic symptoms and related disorders* (SSD) are characterised by physical symptoms that are very distressing or result in a significant disruption of functioning, as well as excessive and disproportionate thoughts, feelings, and behaviours regarding those symptoms. To satisfy such diagnoses, an individual must be persistently symptomatic, that is at least for 6 months [22]. SSD include "Somatic symptom disorder", "Illness anxiety disorder", "Conversion disorder", "Psychological factors affecting other medical conditions", and "Factitious disorder". Compared to the previous editions of the DSM, several important changes have been made in the DSM-5; in particular, "Somatization disorder", "Hypochondriasis", "Pain disorder", and "Undifferentiated SD" have been removed.

The DSM-IV diagnosis of "Somatization disorder" required a specific number of complaints from among 4-symptom groups, while the SSD criteria no longer have such requirement, although somatic symptoms must be significantly distressing or disruptive to daily life and accompanied by excessive thoughts, feelings, or behaviours [22]. Another important change in the DSM-5 criteria is that somatic symptoms do not have to be "medically

unexplained", as it was for many disorders in the DSM-IV. Furthermore, whether or not the somatic symptoms are medically explained, the individual would still have to meet the rest of the criteria to receive a diagnosis of SSD. However, the DSM-5 warns that it is not appropriate to diagnose individuals with a mental disorder simply because a medical cause cannot be found.

The DSM-IV criteria included a large number of overlapping disorders and made it difficult for primary care providers to effectively isolate the problem of their patients. Because those suffering from SSD are primarily seen in general medical settings, the DSM-5 criteria tried to clarify confusing terms and reduced the number of disorders and sub-categories to make the criteria more useful to non-psychiatric care providers [22].

The ICD-10 includes somatic symptoms among neurotic disorders (neurotic, stress-related and somatoform disorders): dissociative (conversion) disorders, somatisation disorder (including hypochondriacal disorders), and other neurotic disorders (among which neurasthenia) [23]. The ICD-10 diagnosis of Somatisation Disorder differs from the DSM-IV for the symptom threshold and for the symptom duration; the DSM-IV diagnosis of BDD coincides with the "Hypochondriacal disorder"; a category of "Somatoform autonomic disorder", characterised by symptoms of autonomic arousal in the absence of any disturbance of structure or function, is also included [23]. The ICD-10 criteria for "Pain disorder" require persistent, severe and distressing pain continuously for at least 6 months. These symptoms, according to the ICD-10, cannot be explained by a physical condition, omitting the mention of "psychological factors" categorically specified in the DSM-IV. Conversion disorder (conversion hysteria) has been renamed and conceptualised as a dissociative rather than a somatic disorder. Finally, differently from the DSM-IV, a diagnosis of "Neurasthenia" is possible in the category "Other neurotic disorders". The revision of ICD-10 is scheduled for 2018.

Both ICD and DSM have been fully criticised for their poor clinical utility. Their main weaknesses are: 1) somatoform disorders are defined on the basis of a failure to find physical causes rather than on the presence of definite psychological and behavioural features; 2) there is a widely and commonly reported discrepancy between the prevalence of these disorders in clinical practice and the frequency of these diagnoses observed in large epidemiologic international research; 3) the major categories of somatoform disorders are rare; 4) the overlap between somatoform disorders and depression and anxiety disorders is an example of the confusion about the boundaries of these disorders; 5) there is evidence that many patients object to the explanatory basis underlying the diagnostic labels of somatoform disorders such as "medically unexplained" and "psychosomatic" [24]. As previously described, the DSM-5 attempted to address this criticism by replacing SDs with SSD and making significant changes to the criteria to eliminate overlap across the somatoform disorders focusing on positive symptoms as well as on the importance of neurological examination. However, the DSM-5 still has a limited clinical utility due to a narrowed capacity to catch the information necessary for the clinical process [25].

The Diagnostic Criteria for Psychosomatic Research (DCPR) were introduced in 1995 to expand the traditional domains of the disease model by translating psychosocial variables that derived from psychosomatic research into operational tools [26]. The DCPR are a set of 12 psychosomatic syndromes whose prognostic role in the development, course, and outcome of physical diseases, regardless of "organic" or "functional" nature, has been largely documented. Eight DCPR syndromes refer to the concept of abnormal illness behaviour: persistent somatisation; functional somatic symptom secondary to a psychiatric disorder; conversion symptoms; anniversary reaction; disease phobia; thanatophobia; health anxiety; and illness denial. The other four syndromes are alexithymia, type A behaviour, demoralisation and irritable mood, which are related to the field of psychological factors affecting medical conditions [26-28]. DCPR includes a semi-structured clinical interview for their assessment [27]. These criteria were found to be more sensitive than those of the DSM-IV in identifying subthreshold psychological distress and in characterising patients' psychological response to medical illness [29]. A recent review of the literature highlighted that the DCPR system can be clinically useful for subtyping medical patients, identifying subthreshold or undetected syndromes, evaluating the burden of medical syndromes, predicting treatment outcome and identifying risk factors [30].

Beyond nosography: psychopathology of somatic disorders

Although neglected by DSM and ICD, several syndromes - which are relatively common in clinical practice - need to be known by clinicians. Such syndromes have been described decades ago, but were later lost in the nomenclature. Here we will describe alexithymia, hypochondriasis, health anxiety, thanatophobia, conversion symptoms and anniversary reaction as examples of somatic syndromes frequent in clinical practice, but often misdiagnosed due to their absence in the DSM and ICD. Interestingly, they are described and included in the DCPR which, thus, represent a useful classification system in clinical practice.

The term alexithymia literally means "lacking words for feelings" and was coined to describe certain clinical char-

acteristics observed among patients with psychosomatic disorders who had difficulty engaging in insight-oriented psychotherapy [31]. Alexithymic patients have deficiencies in emotional awareness and communication, and show little insight into their feelings, symptoms and motivation. When asked about their feelings in emotional situations, they may experience confusion (e.g., "I cannot say"), give vague or simple answers (e.g., "I feel down"), report bodily states (e.g., "my stomach is painful") or talk about behaviour (e.g., "I want to punch the table"). The alexithymia construct was originally conceptualised by Nemiah, Freyberger and Sifneos [32] as encompassing a cluster of cognitive traits including difficulties in identifying feelings and describing feelings to others, externally oriented thinking and limited imaginal capacity. The alternative conceptualisation proposed by Lane and co-workers [33] – alexithymia as a global impairment in emotional processing resulting in limited emotional expression and recognition – has been less influential. Both definitions agree that alexithymia is a deficit, inability, or deficiency in emotional processing rather than a defensive process, and this deficit view is gaining increasing support from basic laboratory and neuroimaging research [34].

Alexithymia was first described in people with psychosomatic disorders, and subsequent research has confirmed elevated levels of alexithymia in people with rheumatoid arthritis, essential hypertension, peptic ulcer and inflammatory bowel disease [35]. Yet, studies have found elevated levels of alexithymia in patients with several other conditions (e.g. cardiac disease, non-cardiac chest pain, breast cancer, diabetes, chronic pain, eating disorders, substance dependence, kidney failure, stroke, HIV infection, fibromyalgia) [36]. The growing recognition that alexithymia is not specific to psychosomatic disorders has led to the view of alexithymia as a risk factor for medical, psychiatric, or behavioural problems that are influenced by disordered affect regulation. Indeed, alexithymia has been associated with failure to use adaptive affect regulation processes such as modulating arousal, appropriately expressing or suppressing emotions, employing fantasy, obtaining and using social support, tolerating painful emotions, cognitive assimilation and accommodation.

Hypochondrium is the uppermost part of the abdomen. The word derives from the Greek term hypokhondrios, which literally means "of the soft parts between the ribs and navel", from hypo ("under") and khondros, or cartilage (of the sternum). Hypochondria in Latin means "the abdomen".

This transference of meaning paralleled changing concepts of pathology, especially in relation to the four humors, until ultimately various mental states came to be associated with changes in the organs of the hypochondria, notably the spleen and the liver. The suffix -iasis denotes an ill process or the condition resulting. It took, however, hypochondria became specifically associated with a morbid preoccupation over health only in nineteenth century.

In 1895 Freud classified hypochondria (with neurasthenia and anxiety neurosis) as an "actual neurosis". This theory has never been satisfactorily explained, nor it has been developed by later analysts. Another approach has been to regard hypochondriasis as due to a disturbance of the body scheme or image. Fisher [37], amongst others, developed assessment instruments for measuring various aspects of this, though his whole impressive concept rests on the rather shaky foundations of classical psychoanalytical theory, projective techniques and self-report questionnaires. French authors introduced the term "coenaesthesiopathy", referring to the sum of organic sensations which are normally vague and in the background, but which give a person his feeling of existence. According to Ey [38], hypochondriasis is a pathological form of human existence, and Ladee [39] gave a phenomenological existential account of hypochondriasis with the experience of decay as a central feature and anxiety as a frequent manifestation.

Although symptoms are diffuse or generalised, one particular symptom or area of concern (such as pain or disturbed sleep) can present as the only complaint, and may occupy patient attention and dominate his life. This monosymptomatic form can vary from a mild preoccupation to a frank delusion. If symptoms of anxiety or depression are present, they are minimal, atypical, difficult to detect, or explicable as secondary phenomena [40]. Pains, particularly muscular ones, are very common. Other common pain syndromes, which may have important psychiatric implications, are backache [41], atypical facial pain [42] and abdominal pain and right iliac fossa pain in females. Interestingly, Kenyon [40] also cited mental pain as a rather vague concept since it may mean just suffering or grief and be close to depression. More recently, mental pain has been more strictly defined as a sense of loss or incompleteness of self and an awareness of one's own role in the experience of emotional pain [43]. Delusions of smell may be the predominant complaint, often attributed to the bowels and usually associated with either paranoid or depressive features [44]. Sometimes, it is halitosis or a more generalised odour, perhaps in conjunction with excessive sweating and anxiety. Symptoms referred to the gastrointestinal tract are common. They can present as vague complaints of nausea, dysphagia, regurgitation, bad taste in the mouth, flatulence, or pain [45]. Aerophagy can be an unrecognised aggravating factor. Preoccupation with bowel function, particularly constipation, can reach extreme degrees; although in this case the correct diagnosis might be bowel obsession syndrome rather than hypo-

chondriasis [46]. It is sometimes difficult to prevent these patients from undergoing repeated investigations or unnecessary surgical procedures. Many anxious and introspective patients complain of palpitations or missing a beat. They sometimes have vague ideas that they have a "tired heart". Patients may also experience a type of inspirational dyspnoea with a feeling that they can never take a really deep and satisfying breath. Some patients are constantly preoccupied with poor hearing which they attribute to "wax", and may spend a lot of time picking at the external auditory meatus or putting in various drops. Others complain of dizziness, vertigo, tinnitus, hearing their pulse beat at night, or general hyperacusis. Nebulous complaints of sinusitis or recurrent sore throats may be met. The feeling of a lump in the throat or globus hystericus may be organically determined [47]. Irritating habits, such as constant sniffing, clearing the throat or cough may be present. A common complaint regarding vision is of "floaters" (muscae volitantes) [40].

Disease phobia, thanatophobia and health anxiety may be part of a hypochondriacal syndrome, yet they may also occur in the absence of other psychiatric disorders. Disease phobia was first described by Bianchi [48] as "a persistent, unfounded fear of suffering from a disease, with some doubt remaining despite examination and reassurance", and Ryle [49] added that it includes also the fear of inheriting or acquiring a disease. According to Fava and Grandi [50], disease phobia differs from hypochondriasis for two characteristics: specificity and longitudinal stability (fears concern a specific disease and are unlikely to be moved on another disease or organ system), phobic quality (fears tend to manifest themselves in attacks rather than in constant worries as in hypochondriasis). Noyes et al. [51] also pointed out that disease phobia often results in the avoidance of internal and external illness-related stimuli, while hypochondriasis usually leads to reassurance-seeking or checking behaviours.

Thanatophobia was described for the first time by Ryle in 1928 [52] as a sense of dying ("angor animi"). It consists of a sudden sense and/or conviction of being on the point of dying without any medical reasons, and may result in the avoidance of stimuli concerning death (e.g., obituary notices, funerals) [53].

Health anxiety includes a variety of worries and attitudes concerning illness and pain, which are less specific than hypochondriasis and disease phobia. Health anxiety differs from hypochondriasis since the former responds to medical reassurance, whereas worries about health may ensue after reassurance in the latter, leading patients to new body-checking behaviours and medical examinations [50].

Conversion symptoms were defined by Engel [54] as ambivalence in symptoms reporting or history of similar symptoms wished on someone else. Lazare [55] observed that conversion symptoms are relatively persistent losses or alterations in sensory or voluntary motor functioning that cannot be explained by known physical disorders or pathophysiologic mechanisms. Examples include paralysis, abnormal movements, aphonia, hypoesthesia, sensations of coldness or warmth, blindness and deafness. A conversion symptom can occur alone, as part of another psychiatric disorder, or as part of a medical or neurologic disorder.

"Anniversary reaction" was first introduced by Hilgard in 1953 [56] to describe the appearance of psychotic symptoms in a woman when her daughter reached the age she had been when her own father died. Thereafter, anniversary reaction was described as an emotional, physical and/or behavioural response triggered by emotionally burdened dates or times [57]. In the DCPR, anniversary reaction is defined as a special form of somatisation or conversion and frequently occurs together with other psychosomatic syndromes [28].

According to the DCPR, other psychosomatic syndromes are noteworthy: persistent somatisation, functional somatic symptoms secondary to a psychiatric disorder, illness denial, "Type A behaviour" and demoralisation [26-28].

Hysteria in the 2000s

Culture and cultural changes deeply affect the way people experience and express their suffering; this is why psychopathology changes over time [58]. An example of this phenomenon is the argument supported by Engel [59] who suggested that the bio-medical model had become a "folk model", with many consequences on clinical presentations of suffering and health care service provision and organisation. Indeed, culture and psychosomatic medicine are so strongly interrelated to become inextricable. This becomes particularly evident for disorders such as somatisation and conversion, due to their complex, predominantly functional pathogenesis, which can only be understood and dealt with assuming a bio-psycho-social perspective.

Hysterical expressions of distress have been conceived as psychodynamically less evolved, or more regressive, than explicit, direct, psychological manifestations. With reference to this, and to the solid interconnection between culture and psychopathology, the study of psychosomatic presentations of distress in a cross-cultural perspective has contributed significantly to a more critical understanding of the deep psychopathological meaning of somatisation and conversion, which were effectively defined as "the black box" of psychopathology [60]. Although large epidemiological studies confirmed that MUPS are similarly vague worldwide and not associated with ethnicity [61], the psychopathology of these clinical manifestations should still be analysed under a cultural perspective. Kirmayer and

Young [62] effectively argued that "psychological theories of somatization focused on individual characteristics must be expanded to recognize the fundamental social meanings of bodily distress". In cultures where "the harmony of the family and group is more important than individual anatomy", somatisation might be a refined superior way to "have one's cake and eat it too", a legitimate and codified pattern of expressing suffering [63]. Then, when individual cultural milestones change, for example as a result of migration, this inevitably reflects on psychopathology, explaining why clinicians in Western societies often believe that hysteria "is back" as a typical disorder of migrants [64]. Clinical cases have been described supporting this issue, though the hypothesis still needs to be confirmed on an epidemiological basis and analysed deeply as a gateway to the understanding of the process of somatization.

Hysteria, which as previously described was acknowledged as a neurological condition in the 19th century and then become a psychiatric disorder with the DSM, is "back in the arms" of neurologists in current clinical practice since these patients are still too often referred to neurologists [65]. However, advances in contemporary psychosomatic research are providing neuropathological explanations of hysteria [66]. This new knowledge has triggered a cultural change, with further feedback on psychopathology. On one – positive – side, it has decreased stigma against mental disorders and individuals are more incline to acknowledge their psychic distress as relevant as well as the connection between psychic and somatic symptoms. On the other, the diffusion of basic medical knowledge in the population has introduced some problems. Patients have access via internet to abundant information on disorders, medications and healthcare services. They are exposed to countless real and fictional medical accounts that create expectations and resistance. All this impacts on the psychopathology of somatisation and conversion symptoms, with clinical presentations that are sometimes more difficult to be clearly recognised in their functional nature, or more "aggressive" attitudes of patients in the diagnostic and therapeutic process. New psychopathologies are described, in which very often a common feature is the pathology of the mind-body relationship that reminds conversion and/or somatisation, for example multiple chemical sensitivity or orthorexia/vigorexia. Similarly, contemporary life styles may be in a circular relationship with the psychopathology of histrionic personality disorder, which is frequently associated with SSDs. Features such as excessive emotionality, attention seeking, tendency to dramatisation, seductivity and suggestibility, typical of this personality construct, appear to be more frequent in the general population, configuring a social phenomenon [58].

In brief, cultural changes may contribute to creating new illnesses, but advances in psychosomatic medicine have contributed to the understanding of complex aetio-pathological pathways and disentangle the interrelationship between health and culture, opening the way to new and effective therapeutic strategies. New challenges, and new opportunities, in diagnosis, clinical management and therapy have been proposed [66]. Innovative organizational care models, based on trans-disciplinarity are needed. Interesting tools for the assessment of bio-psycho-social complexity are the INTERMED method by Wild and coworkers [67] and the already mentioned DCPR [26].

Conclusions

In 1960, G. Engel [68] criticised the concept of disease: "The traditional attitude toward disease tends in practice to restrict what it categorizes as disease to what can be understood or recognized by the physician and/or what he notes can be helped by this intervention. This attitude has plagued medicine throughout its history and still stands in the way physicians fully appreciating disease as a natural phenomenon". The inadequacy of the concept of disease particularly applies to medical symptoms that are not explained by organic disease or abnormal laboratory testing. Such symptoms may be transient without requiring medical attention, or may be a cause of concern, disability and excessive healthcare costs [69]. These symptoms can be attributed to somatisation, defined by Lipowski [70] as the tendency to experience and communicate psychological distress in the form of physical symptoms and to seek medical help for them. Anything that cannot be explained by organic factors, with special reference to laboratory investigations, is thus likely to fall within the domains of somatisation. The DSM-IV represented the effort of classifying such symptoms according to their clustering and characteristics. The DSM-5 emphasises diagnosis made on the basis of positive signs and symptoms rather than the absence of a medical explanation for somatic symptoms. However, the DSM-5 maintains the old logic that if it is not organic, it is psychiatric. In this review, we have tried to describe somatic disorders on the basis of their psychopathological manifestations rather than on the basis of the traditional nosography, with the specific aim to give clinicians useful tools to obtain a correct diagnosis, and not to reach it via a long way encompassing the exclusion of any other organic or psychiatric disorder.

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Behavioural addictions and the transition from DSM-IV-TR to DSM-5

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Summary

The concept of addiction, traditionally applied to psychotropic substances, has been officially extended by the DSM-5 to gambling disorder, a "behavioural addiction" (BA), in which the focus of the addiction is represented by a specific behaviour. BAs are emerging psychopathological disorders with an increased in scientific interest and socio-cultural and economic implications. In this paper, we will review the available evidence on the clinical, diagnostic and psychopathological features of BAs, with particular reference to gambling disorder, sex-addiction, compulsive buying, exercise, work, technological and love addictions. Even though each of these addictions may likely meet the requirements for classification as a separate diagnostic entity, at present, the only two disorders included in DSM-5 are gambling disorder and internet gaming disorder. The absence of specific diagnostic criteria, the present of difficulties in differentiating pathological from "normal" behaviours, and blurring of demarcation lines between physiology and pathology complicate the epidemiologic investigation and diagnostic assessment of BAs. Moreover, the lack of valid screening tools and the frequent comorbidity with other mental disorders further hinder the diagnostic approach to BAs. Therefore, clear-cut and well-defined diagnostic classification needs to be established, along with a better understanding of the clinical and psychopathological features of BAs, as a fundamental prerequisite to prevention, early diagnosis and treatment.

Key words

Behavioural addictions • Psychopathology • Diagnosis • Clinical features

Introduction

The concept of addiction, for years adopted solely to indicate the use of psychotropic substances, is nowadays frequently applied to describe a heterogeneous group of syndromes known as "behavioural addictions", "no-drug addictions" or "new addictions" [1]. Prevalence rates for such conditions, taken as a whole, are amongst the highest registered for mental disorders with social, cultural and economic implications. Individual forms of BA are linked by a series of psychopathological features, thus supporting the initial proposal, subsequently rejected, to devote a chapter to these disorders in the DSM-5. These include: repetitive, persistent and dysfunctional behaviours, loss of control over behaviour in spite of the negative repercussions of the latter, compulsion to satisfy the need to implement the behaviour, initial wellbeing produced by the behaviour, craving, onset of tolerance, abstinence and, ultimately, a progressive, significant impairment of overall individual functioning [2 3].

A progressive loss of control over the specific behaviour may result in a consequent neglect of interpersonal relationships, and abandonment of roles and activities previously seen as important. At the same time, negative health consequences may be manifested, including onset of sleep disorders, weight gain, functional somatic symptoms and even suicidal behaviours [1].

For the first time, the DSM-5 chapter "substance related and addictive disorders" includes gambling disorder, previously classified as an impulse control disorder [4]. A form of internet addiction, another BA, is listed in Section 3 of the manual as an "internet gaming disorder", among conditions requiring further investigation. However, numerous other BAs have been described in the literature: sex-addiction [5], compulsive buying [6], exercise addiction or overtraining syndrome [7], love addiction [8], work addiction or workaholism [9] and technological addictions [10]. Bearing in mind that a vast range of routine behaviours might potentially show the characteristics of an addiction, numerous authors have raised the issue of the implied risk of over-pathologising such behaviours [1 11]. In fact, most BAs were omitted from the DSM-5 due to insufficient evidence, poor description of the clinical course of the behaviour and the need to establish diagnostic criteria in order to classify these behaviours as mental disorders [12]. In addition, several authors believe that BAs are largely

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manifested secondary to other mental disorders, such as mood, anxiety and personality disorders, and should not therefore be classified as separate diagnostic entities [11].
In view of their characteristic features, BAs have been likened to substance-related, obsessive-compulsive and impulse control disorders [2 11].
The idea of incorporating BAs into the area of substance-related disorders stemmed from the robust body of clinical, neurobiological, neuropsychological, biochemical and genetic findings, supporting the significant associations and similarities between the two classes of disorders, on the basis of which a common biopsychosocial component has been hypothesised [13 14]. BAs and substance-related disorders appear to be based on an impairment of the three functional systems of motivation-reward, regulation of affect and behavioural inhibition [13]. This impairment, in turn, elicits the urge to behave in a manner capable of activating the reward circuitry or avoiding discomfort, ignoring the negative implications associated with the specific behaviour. The so-called "incentive sensitisation theory" has been purported to underlie the onset of substance use disorders and, more recently, BAs, including gambling disorder. The latter represents a drug addiction development model according to which the addictive behaviour, in the same way as the stimuli associated with dysfunctional behaviours alter the sensitivity of the mesocorticolimbic dopamine system involved in reward and reinforcement of response, produces an increased sensitivity on the repeated administration of drugs and/or repeated exposure to specific contexts and stimuli [15]. The associated mental and sensorial events are themselves seen as pleasurable and, thus, act as an incentive to implement the behaviour.
The scarce data available in literature on the longitudinal course of BAs tend to highlight an episodic rather than a continuous course, compared to that observed with traditional substance-related addictions [1]. Although subjects rarely tend to seek help for their problems, individuals who do so tend to refer to healthcare professionals, possibly as they realise they are suffering from a medical problem, rather than merely attributing their problems to an inappropriate lifestyle [1].
Given the increasing interest in the field, the aim of this paper was to review the available literature related to the clinical-diagnostic and psychopathological features of the main BAs, with particular reference to gambling disorder, sex-addiction, compulsive buying, exercise addiction, work addiction, technological addictions and love addiction.
The increasing scientific focus on these disorders dictates the need for a clear-cut and well-defined diagnostic classification and a better understanding of the psychopathological features, representing a fundamental prerequisite in prevention, early diagnosis and treatment.

Methods

A systematic review of the PubMed database was conducted using the following keywords: "behavioral addictions", "gambling" "sex-addiction", "compulsive buying", "exercise addiction", "work addiction", "internet addiction", "technological addiction" and "love addiction". Studies published in English or Italian up until July 2015 were evaluated, and studies focusing mainly on psychopathological and clinical-diagnostic aspects were selected. Each condition is herein briefly presented and its main psychopathological and diagnostic features summarised.

Compulsive buying

Compulsive buying (CB) or compulsive shopping is a disorder first described at the end of the 19th century by Kraepelin as "oniomania". Despite the large quantity of data available in literature, there is still need for further understanding and recognition of CB, frequently neglected in the clinic in spite of the high prevalence observed, particularly in the young, and largely female, population [3 6 16-18]. In the absence of formal diagnostic criteria, diagnosis of CB is based on a careful clinical assessment of buying habits, feelings and associated thinking. The disorder is manifested with a recurrent and irresistible compulsion to purchase useless or superfluous items that go far beyond the financial possibilities of the buyer. Thought content is polarised on buying, with an uncontrollable urge to implement the behaviour and a tendency to lose control. A condition of extreme pleasure and well-being is described as the subject completes the purchase, whilst tension rises if the transaction is not completed. This consequently results over time in a feeling of guilt and shame, as the subject recognizes the implications associated with the behaviour. The feeling of pleasure is achieved by purchasing, selecting and ordering the item, rather than through using it. It should be taken into account that the majority of subjects subsequently casts aside, donates or discards the items purchased [17 18]. The urge to buy tends to be repeated with a frequency ranging from hours to weeks or months. In almost all cases the disorder has serious repercussions on the subject' social and family life and finances [18]. CB as a primary disorder should be distinguished from the excessive spending manifested in the context of other psychiatric disorders, including bipolar disorders, anxiety disorders, psychosis or dementia [3]. CB should, moreover, be distinguished from the impulse to buy manifested as an occasional loss of control in the presence of an overwhelming desire for a particular item [17 18]. Women tend to buy items of clothing, cosmetics and jewellery, whilst men opt for electronic gadgets or car accessories [3]. In some cases,

the subject diversifies the type of purchase, while in others focuses largely on the same type of product. Some prefer to buy on the Internet, from the TV or in shopping malls, while others prefer exclusive boutiques; some buy for themselves, others tend to buy gifts for relatives and friends [18]. CB is frequently manifested in comorbidity with other mental disorders, including anxiety disorders, compulsive hoarding, obsessive-compulsive disorder, substance abuse, intermittent explosive disorder, pathological gambling, exercise dependence, pathological internet use, binge eating disorder, bulimia and personality disorders [6 18].

The initial symptoms of the disorder are generally manifested between the ages of 20 and 30 years, frequently in subjects with low self-esteem, perfectionists or narcissists, while associated problems are often manifested later, following the accumulation of debts, family conflicts and other psychosocial consequences correlated with this inappropriate behaviour [6 18].

Sex-addiction

Sex addiction (SA) or impulsive-compulsive sexual behaviours are characterised by a prominent role of sex in the everyday life of affected patients. They feel a compulsion to satisfy their sexual urges and lose control, overlooking the serious consequences produced on their personal health, on the toll it takes on relationships, and at times even legal issues [3 5 17 19]. Over the years, a series of authors has proposed specific diagnostic criteria to reliably identify SA [20]. However, the proposal to include hypersexual disorder in DSM-5 was rejected due to the paucity of data available in support of a specific diagnosis.

Sex addicts are on the constant lookout for exciting situations, or situations capable of providing an opportunity of no-ties sexual encounter, frequenting multiple sexual partners or engaging in compulsive masturbation. Sexual activity is partly aimed at attenuating the condition of distress that precedes the behaviour, and is subsequently replaced by a sense of guilt and shame. As a result of these feelings, the subject becomes increasingly introverted, ultimately manifesting an impaired functioning and lower quality of life, that merely serves to perpetuate and reinforce the addiction, the consequences of which are frequently underestimated. The time spent in seeking, undertaking and recovering from sexual encounters induces the subject to neglect all other activities. Tolerance and abstinence may be present, accompanied by emotional lability and irritability if subjects are not able to satisfy their sexual needs. The term impulsive-compulsive sexual behaviour has been used in referring to SA, as an impulsive component (pleasure, excitation, or reward) is involved at the start of the cycle, and a compulsive component perpetuates the behaviour [5 19]. Comorbidity with other mood disorders, anxiety disorders and substance abuse has been reported [19].

Work addiction

Work addiction (WA) or "workaholism" was first identified in 1971 when Oates used the term "workaholic" to refer to a subject who experiences a compulsion or uncontrollable need to work unrelentingly. As we live in a society in which an excessive commitment to work is viewed as a positive quality, this disorder is frequently under-diagnosed. A workaholic should, however, be distinguished from a normal, work-engaged individual: the former is driven to work compulsively, with disastrous consequences for his/her physical and mental health; the latter is a highly motivated individual who obtains deep satisfaction from his/her work. Accordingly, the difficulty of defining the WA construct clearly emerges, particularly due to the numerous definitions provided, a lack of full understanding of the phenomenon, and the difficulty to establish a boundary between normality and a pathological condition [9]. Similar to previous editions, DSM-5 fails to mention this disorder, considering it merely a symptom of an obsessive-compulsive personality disorder in which the individual manifests an excessive commitment to work and productivity, even forsaking leisure activities and friendships [4]. With this form of addiction, the individual tends to seek an indirect pleasure from work. Indeed, it would seem to be the social implications, power and success rather than the working activities *per se,* to produce pleasure and addiction, thus being sought after by the subject in an attempt to improve his/her public image and increase his/her self-esteem. Work addicts experience a strong urge to devote their life and time to work, which ultimately takes over every minute of the day, causing them to neglect or abandon their family and personal life, with heavy repercussions on social functioning [9]. On non-work days, such as the weekend or bank holidays, when patients are unable to carry out working activities, they are generally pervaded by a sense of anguish, emptiness, boredom, irritability and anxiety [3]. Non-work activities, or activities unrelated to the individual's work, are avoided and scorned. Thought content is dominated by work-related issues, relationships and potential mistakes, both real and imaginary. The most significant and frequent short-term implications are related to family life and relationships with colleagues [9]. In the previous contexts, the individual displays an authoritarian manner, aggressiveness, continued tension, excessive self-confidence, poor tolerance to criticism, bluntness, lack of affectivity and cognitive rigidity [3]. In the long-term, additional mental and physical disorders, such as

cardiovascular diseases, may be manifested. Over time, the individual's professional standing may be negatively affected due to a loss of efficiency and productivity.

Love addiction

Love addiction (LA) is characterised by a pattern of maladaptative romantic relationship issues that results in a significant impairment of functioning and/or a state of marked distress [8]. LA can be distinguished from love passion, as the desire for the other person represents a compulsive need, with pain taking the place of pleasure, and the individual choosing to continue with the relationship although fully aware of the negative consequences this may entail [8]. The partner represents one of the main reasons for existing, and his or her absence, even on a temporary basis, determines an intense sense of emptiness and anguish [3]. Love addicts are completely devoted to the partner, privileging his or her wellbeing over their own, often neglecting social and family relationships, work and leisure activities [8]. In many cases, the partners are difficult individuals affected by mood swings, pathological addictions and impulse control disorders, who frequently lack respect, have different needs and are devoid of life projects [3]. Affected subjects may occasionally admit their relationship problems, but they are incapable of escaping from them, at times underestimating the toll the relationship is taking in an attempt to justify their actions. Anxiety, depression, feelings of guilt, hyper-reactivity, irritability, jealousy and possessiveness may be manifested, even extending to paranoid ideation, which may progress into an overt psychotic syndrome with risk of aggressive behaviours [3].

Gambling disorder

Gambling disorder (GD) is characterised by persistent and maladaptive gambling behaviour, whereby individuals engage in frequent and repeated episodes of gambling despite serious adverse consequences.

The DSM-5 included GD in the diagnostic category of 'Substance-related and Addictive Disorders' [4]. Pathophysiological models for drug addiction were therefore considered to be relevant to GD and affected patients, who may benefit from therapeutic approaches used to treat SUDs [21]. There is strong evidence suggesting that similar predispositions (genetic, environmental and social) influence the development and maintenance of GD and addictive disorders. Also, like SUDs, GD presents the phenomena of tolerance, withdrawal and craving.

GD subjects have significantly more Axis I disorders than controls, with higher rates of bipolar disorder, and it has been suggested that mood and anxiety disorders often precede gambling problems [22]. In addition, a recent longitudinal, prospective study found that subjects who reported past-year disordered gambling were significantly more likely to have new onset of Axis I psychiatric disorders [23]. According to the *National Epidemiological Survey on Alcohol and Related Conditions*, around 70% of pathological gamblers had a lifetime alcohol use disorder [24]. In pathological gamblers, the co-occurrence of other mental disorders increases the likelihood of treatment-seeking, though it may be the case that GD subjects are more likely to seek treatment for their comorbid disorders rather than for their gambling problems, which thus go undetected [25].

Urge to gamble is often associated with arousal and restlessness or with tension and anxiety. Various forms of emotional and mood disturbance are associated with divergent motivations that might represent distinct pathways into gambling behaviour [26]. GD patients who experience hypomanic symptoms report stronger motivations to gamble as a means to regulate mood, more frequently to gain pleasure and enjoyment. Depressive symptoms are also a very common finding among pathological gamblers, and evidence suggests that they are closely related to engagement in gambling. Depressive symptoms possibly provide an impetus to console or comfort oneself through gambling, as an attempt to relieve a negative mood [27].

Consistent with an addiction model, it has been proposed that gamblers who experience high levels of anxiety engage in gambling activities to reduce arousal states. Furthermore, anxiety symptoms have been considered as part of withdrawal-like symptoms in GD [28]. Moreover, specific temperamental (novelty seeking) and character (self-directedness and cooperativeness) dimensions differentiated probable pathological gamblers from both non-pathological gamblers and controls [29].

Impulsivity is a hallmark of GD, which is also characterised by compulsive features. Studies indicate that pathological gamblers score highly on specific measures of compulsivity, and it seems that, over time, impulsive habits may shift toward a more compulsive pattern of behaviour. Behaviours in GD patients are often repetitive and hard to suppress. Additionally, most published findings suggest heightened response perseveration in GD.

Craving phenomena, defined as the subjective urge to consume a drug or behave in a certain way, and abnormal cue reactivity are central to addictive behaviours and may promote relapse. As in all substance addictions, craving is a key symptom of GD as well. In fact, research on relapsing precipitants suggests that craving is one of the main factors to provoke and maintain episodes of gambling.

Finally, growing evidence suggests that GD patients are

characterised by significant neurocognitive impairment in a variety of domains, and it has been proposed to devise treatment strategies that specifically target cognitive symptoms. Pathological gamblers often have difficulty shifting their thoughts and behaviour away from gambling. Enhanced cue reactivity and attentional bias to gambling cues have been reported in GD, along with increased reward-seeking behaviour and lowered reward sensitivity. Pathological gamblers have difficulty filtering irrelevant information and inhibiting ongoing responses. Decision-making and executive functions were also shown to be compromised. Moreover, GD patients are characterised by deficient motor response inhibition and impaired cognitive flexibility [30].

Subtyping pathological gamblers based on personality domains, impulsivity, depression and anxiety comorbidity has been proposed [25]; however, more research is needed to provide support for these models and further investigation warranted to better understand how psychopathological dimensions impact the clinical presentation and treatment outcomes of GD.

Internet addiction

Over the last decades, Internet has become an integral part of daily life for most individuals and internet users across the world have grown to over two and a half billion. The increase in Internet use has been paralleled by the emergence of psychopathological features of addiction linked to its use. This phenomenon is growing both in prevalence and within public consciousness as a pathological condition, which has been variously referred to under different terms [5], particularly Internet addiction (IA). Extensive data clearly indicate that dysfunctional Internet use has the potential to bring about considerable psychological distress, and there has been a substantial increase in the number of IA service providers in many countries. As yet, IA remains an ill-defined and heterogeneous construct, owing to the inconsistent methodological approaches used to study it, varied use of terminology and lack of standardised diagnostic criteria. IA may be broadly defined as a use of the Internet that interferes with the individual's health and creates psychological, social, school and/or work difficulties [31].

The diagnosis of IA does not appear in any official diagnostic system. Recently, however, the DSM-5 has singled out Internet Gaming disorder (IGD), defined as compulsive/uncontrolled gaming online that jeopardises professional and/or social functioning, and categorised it as a condition for further study (Section III) [4].

It has been reported that 88.3% of individuals with IA have an average of two other co-occurring diagnoses [32] and there is currently some debate over whether IA reflects a BA or is secondary to other psychiatric disorders. Some authors argue that most individuals presenting with IA are using it as a medium to fuel other addictive behaviours and that IA may be more appropriately conceptualised within existing psychiatric disorders [33]. However, accruing evidence supports the notion that IA is a separate psychiatric entity, with strong parallels to existing recognised disorders. Numerous authors have, in fact, proposed it to be an impulse-control disorder or an addictive behaviour [2 34]. In the latter view, IA is regarded as a BA, as Internet use may produce short-term reward that engenders persistent behaviour, despite knowledge of adverse consequences. IA shares some general aspects with other BAs, such as loss of control on experience, tolerance, withdrawal and the appearance of an overwhelming need, similar to craving, to repeat the experience. In line with this understanding of IA as a BA, Block [35] suggested 4 diagnostic criteria for IA: (1) excessive Internet use, associated with loss of sense of time or neglect of basic drives; (2) withdrawal, including feelings of anger, depression and tension when Internet is not accessible; (3) tolerance, including the need for better computer equipment, more software, or more hours of use; and (4) adverse consequences (e.g., sleep deprivation, marital difficulties, lateness for early morning appointments, neglect of occupational duties).

Young considers IA as a continuum in which Internet users progress gradually from no or modest symptoms to exhibiting extreme pathological behaviours and defines problematic non-essential Internet usage (non-business/non-academic) resulting in significant impairment or distress by the presence of five (or more) of the eight items on the Diagnostic Questionnaire [36].

There is growing evidence that genetic factors, neurobiological alterations and specific personality traits influence the development of IA. Structural and functional brain reorganisation is thought to contribute to the development of addictive behaviours, including IA, which, in fact, was found to be associated with abnormal interactions between brain regions [37]. Abnormalities in serotonin transporter genes have also been correlated with IA, suggesting similar genetic traits with depressed patients [38]. Furthermore, a growing body of neuroimaging studies shows that the prefrontal cortex plays a significant role in the development of IA [39], as in other addictive disorders. Personality traits of high harm avoidance, high novelty seeking, high reward dependence, low self-directedness and low cooperativeness were positively correlated with IA. Lack of perseverance was found to predict IA. Moreover, a significant association between excessive use of violent Internet video games and aggressive behaviour has also been observed [40]. Recent studies have also identified moderating factors, such as coping styles and Internet ex-

pectancies that determined functional and dysfunctional Internet use among adult populations [39]. In this view, Internet use may represent a coping strategy that takes the form of reassurance, avoidance, relief of dysphoric symptoms and compulsion in problematic use. IA can thus be conceptualised as a form of maladaptive self-regulatory strategy. Differences in automatic and controlled aspects of self-regulation have, in fact, been linked to IA [31].

In conclusion, the study of IA is currently hampered by ambiguous definitions of the phenomenon and a diversity of diagnostic and prognostic criteria, the expansion of this area of distress and the consequent increase in clinical observations, raise issues concerning its management. Many patients refer to clinicians who do not dispose of standard clinical treatment protocols but only of limited data from case studies. Also, pharmacological and psychotherapeutic treatments specific to IA have received limited testing in large, rigorous studies [41]. More research is, therefore, needed on areas that remain unclear and contribute to the prognosis of IA, including the temporal relationships with comorbid disorders and the psychological changes that occur through Internet use, such as disinhibition and increased risk-taking.

Technological addictions

Technological addictions involve human-machine interaction. They can be passive (e.g., television) or active (e.g. computer games) and usually contain inducing and reinforcing features, which may contribute to the promotion of addictive tendencies. The category of technological addictions is not mutually exclusive and contains conditions that could be considered under other kinds of addiction (e.g., telephone sex addiction likely better explained as sex addiction).

Information and Communication Technologies (ICTs) are a hallmark of today's societies. The major factors that foster the ICT use to get in touch with other people are accessibility, availability, intimacy, high stimulation and anonymity. Clinical evidence of overuse in numerous subjects, in some cases with symptoms similar to those of addictive disorders, has been reported [42]. Technological addictions may be particularly relevant to adolescents, a population with great vulnerability to addiction. Indeed, teenagers have less impulse control, poorer long-term planning, and tend to minimise the risks of potentially dangerous behaviours. This is due primarily to cortical immaturity, particularly in the prefrontal cortex. Additionally, adolescence is a period during which individuals develop personal independence from adults [43]. ICTs support this independence in that the younger generation is more comfortable with these tools, which provide access to social relationships that teenagers find particularly important.

Most technological addictions involve the Internet, mobile phones and video games. However, the accessibility of new technologies, like cell phones, which have the advantages of portability and an ever growing array of functions, makes their over-use increasingly likely. In fact, these tools are gradually more interrelated, to the extent that it is possible to connect to a social network via a mobile phone as well as play a game online.

The personality trait most consistently associated with problematic mobile phone use is low self-esteem, though extraversion is associated with more intense use. Women with low self-esteem are the most vulnerable group, and the most commonly associated psychopathological symptom was depression [44]. A recent report found that materialism and impulsiveness drive both a dependence on cell phones and instant messaging [45].

Technological addictions, despite their short history, have clinical, social, and scientific support for inclusion within addictive disorders [33], although they may still require additional research before this is reflected in diagnostic manuals.

Proposed diagnostic criteria for the abuse of the Internet, mobile phones and video games are as follows: 1) tolerance: need for increased use of the technologies over time; 2) withdrawal: emotionally intense discomfort when spending an unusual length of time without using the technology or when use is disrupted; 3) greater use than intended when beginning a session; 4) desire to stop the use of the technology without being able to do so; 5) spending too much time engaged in activities related to the technologies; 6) stopping other activities in order to increase use of the Internet, mobile phones, or video-games; 7) continued use of the Internet, mobile phones, or video-games despite an awareness that such use is causing damage.

With regard to social networks, young people's exposure to social network sites such as Facebook is increasing, along with the potential for such use to complicate romantic relationships. Recently, Facebook intrusion was linked to relationship dissatisfaction, via jealous cognitions and surveillance behaviors [46].

However, ICT overuse can be a symptom of an underlying mental disorder and a way to cope with emotional distress. Risk and protective factors need to be considered to explain the vulnerability of some people. In addition, future studies would enable better understanding of the damaging effects that ICT overuse may have on social functioning in the real life.

Exercise addiction

Physical exercise and sports activity are of benefit and their regular practice may be both physically and mentally beneficial. However, when exercise becomes ex-

cessive it can lead to physical and even psychological damage. As a consequence, the loss of control renders the behaviour pathogenic and potentially addictive. A variety of expressions is used to describe this addiction as exercise dependence, obligatory exercise, compulsive exercising, exercise abuse, compulsive athleticism and anorexia athletica.

Research into highly accustomed exercise started with the study of Baekeland who, despite offering payment, faced great difficulties in recruiting committed athletes for participation in his study about exercise deprivation. In 1976, William Glasser coined the term "exercise addiction" (EA), describing the many positive benefits of exercise such as relaxation, exaltation and satisfaction (calling it "positive addiction"). De Coverley Veale subsequently proposed a differentiation between primary and secondary EA, intending the latter just like a symptom of eating disorders. High levels of obligatory physical exercise were found in the context of eating disorders, supporting the model of secondary dependence [47]

Actually, the term "exercise addiction" incorporates elements of both dependence and compulsion. Subsequent studies have focused on the harmful consequences of the condition: obsessive need to increase exercise levels, overuse distress, interference with work and family life and incapacity to reduce the level of exercise [47].

In DSM-IV-TR, excessive exercise is defined as exercise that "significantly interferes with important activities, occurs at inappropriate times or in inappropriate settings, or when the individual continues to exercise despite injury or other medical complications". As for other forms of BAs (e.g., compulsive buying, sexual addiction, 'workaholism'), physical EA has surfaced in the medical literature in the last years, but it is not considered in the DSM-5.

On one hand, EA can be conceptualised within the obsessive-compulsive spectrum as physical activity, but it might also be an obsessive/compulsive symptom to relieve feelings of distress [48]. On the other hand, it has also been highlighted that addicted exercisers show behavioural patterns as withdrawal symptoms, mood modification, tolerance, relapse, impulsivity, conflict and tendency to return to excessive activity after periods of abstinence, as well as physical, social and financial adverse consequences [49].

A definition of EA was proposed by Hausenblas and Downs [50]: "a maladaptive pattern of excessive exercise behaviour that manifests in physiological, psychological and cognitive symptoms". They described exercise addiction based on the modified version of the DSM-IV-TR criteria for substance dependence:

- *tolerance*: increasing the amount of exercise in order to feel the desired effect, being it a "buzz" or a sense of accomplishment;
- *withdrawal*: in the absence of exercise the person experiences negative effects such as anxiety, irritability, restlessness and sleep problems;
- *lack of control*: unsuccessful attempts to reduce exercise level or cease exercising for a certain period of time;
- *intention effects*: unable to stick to one's intended routine, as evidenced by exceeding the amount of time devoted to exercise or consistently going beyond the intended amount;
- *time:* a great deal of time is spent preparing for, engaging in and recovering from exercise;
- *reduction in other activities*: as a direct result of exercise, social, occupational and/or recreational activities occur less often or are stopped;
- *continuance:* continuing to exercise despite knowing that this activity is creating or exacerbating physical, psychological and/or interpersonal problems.

There are various questionnaires assessing EA and there is a large variability to ascertain its prevalence, as a result of using different questionnaires or criteria for assessment. Studies also tend to focus on diverse and often unspecified types of physical activity.

Concerning the neurobiological mechanisms, several hypotheses have been formulated to explain physical exercise addiction: the *affect regulation hypothesis* proposes that physical activity serves as a "positive affect enhancer" and a "negative affect reducer", registering the reduction of anxiety and depression as a purpose among runners [51]. The *sympathetic arousal or habituation hypothesis* is a physiological model that suggests how the habitually exercising individual is motivated to increase the level of arousal: adaptation to exercise reduces the sympathetic activity, meaning lower level of arousal. This condition may be felt as a lethargic or energy-lacking state by the subject, who increments not only the frequency but also the amount of exercise in order to increase his/her arousal [52]. The *endorphin hypothesis* suggests that there may be a relationship between the stimulation to release endorphin and endogenous opioid peptides and vigorous exercise. The exercise-induced changes in psychological function may be the result of alterations in endogenous opioid system. Moreover, induced IL-6 cytokine causes an anti-inflammatory response likely linked with the developing of exercise addiction (*cytokine hypothesis*) [53]. Elevated levels of catecholamine have been found during and following exercise and introduce the *catecholamine hypothesis* of exercise dependence [54]. As others behaviours, physical exercise may stimulate the dopamine reward system. Several lines of data, moreover, highlight the involvement of multiple common neurotransmitter systems (e.g., serotonergic, dopaminergic, noradrenergic, opioidergic, glutamatergic) in the pathophysiology of EA.

Discussion

The current knowledge and literature on BAs continue to evolve. Although a large body of literature is available for some disorder (i.e., gambling disorder), for others the available data are often quite anecdotal. The specific characteristics of each of the above mentioned disorders appear to justify their inclusion as a separate diagnostic entity, although, at present, the only two disorders included in DSM-5 are gambling disorder, in the chapter "substance related and addictive disorders", and internet gaming disorder, in Section III of the Manual, listed among conditions that require further investigation [4]. The initial proposal to include a chapter on BAs in DSM-5 was not adopted, indicating that, at the present time, clinical data for such a step are not sufficiently robust. Nevertheless, gambling disorder was inserted as the sole BA, in the chapter of substance-related disorders. This increased openness displayed by the DSM-5 classification of gambling disorder as a BA, rather than an impulse control disorder as in DSM-IV-TR, seems to open new avenues for additional research in the field [1]. Support for reclassifying gambling disorder in DSM-5 has stemmed from several studies in the field of neuroimaging and pharmacological treatment that documented specific involvement of neurotransmitters and receptors and therapeutics known to be involved in substance addictions [55]. Nevertheless, the increasing scientific interest focused on other BAs dictates the need for a clear-cut and well-defined diagnostic classification and a better understanding of the psychopathological features as a prerequisite to prevention, early diagnosis and treatment. The lack of valid specific psychometric tools and frequent comorbidity with other mental disorders further hinders the diagnostic procedure, and complicates epidemiological surveys to assess the real prevalence of a specific BA across different countries and cultures. Even epidemiologic surveys may not be sufficient to support the inclusion of a potential BA in current classification systems. In the case of compulsive shopping, for instance, epidemiologic surveys over the last decade [16] did not result in inclusion in the DSM-5. On one hand, the tendency to classify an increasing number of BAs, and to medicalise these behaviours, is considered by many experts particularly worrisome, such that several authors have suggested that in many cases the behaviours manifested do not represent a series of primary symptoms, but rather symptoms secondary to other mental disorders such as anxiety disorders, mood disorders, personality disorders and ADHD [1 11]. On the other hand, the possibility to demonstrate that, at least for some subgroups of patients, BAs can produce measurable functional impairment and reduction of quality of life would help differentiate them from normal behaviours and support their diagnostic classification. Accordingly, an improved definition of these disorders should be established using uniform diagnostic criteria and following the development of valid screening tools to facilitate the diagnosis and understanding of the correlations between BAs and other psychiatric disorders, both in terms of differential diagnosis and analysis of the frequent comorbidity detected in these subjects. Moreover, in view of the current scarcity of clinical data for most BAs, further studies focusing on longitudinal course, gender implications, help-seeking behaviours, risk factors and protective factors, as well as response to pharmacologic and psychotherapeutic interventions, are needed [1 3].

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Psychopathology of dual diagnosis: new trumpets and old uncertainties

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Summary

People suffering from severe mental illnesses, such as schizophrenia and major affective disorders, have high rates of addictive behaviours related to alcohol and illicit substance use. This overview summarises new and old psychopathological issues on the comorbidity between mental and substance use disorder, the so-called 'dual diagnosis' phenomenon. It represents an unanswered challenge in terms of pathogenic models, treatment and long-term clinical management. Dual diagnosis is a complex and heterogeneous entity and a number of explanatory models of substance use among people with severe mental disorders have been proposed, aiming to test the 'self medication' hypothesis, the potential aetiological role of substance on occurrence of mental disorders, and the common underlying environmental, genetic and biological factors. Furthermore, in the literature attempts have been made to clarify psychopathological characteristics of people who suffer from dual diagnosis. Individuals with dual diagnosis appear to be more often males, with an earlier onset of the mental disorder and more severe clinical and social outcomes. The co-occurrence of mental and substance use disorders complicates treatment, management and prognosis of both disorders, but it remains often unrecognised and undertreated. Mental health and addiction professionals should accurately assess and evaluate this comorbidity, although aetiological links, temporal relationships and psychopathological characteristics are still not entirely clear and, probably, heterogeneous and multifactorial.

Key words

Psychopathology • Dual diagnosis • Comorbidity • Severe mental disorders • Addiction

Introduction

The term *dual diagnosis* has been historically used to define the co-occurrence of mental and substance-related disorders in the same individual. Since the late 1980s, addictive behaviours related to alcohol and illicit substance use have been shown to be highly prevalent in people suffering from severe mental illnesses, such as schizophrenia and major affective disorders [1]. The dual diagnosis phenomenon is a key psychopathological issue, representing an unanswered challenge in terms of pathogenic models, treatment and long-term clinical management. Research in clinical populations with dual diagnosis is consistent in showing poor clinical and social outcomes [2]. Individuals who suffer from both mental illnesses and substance use disorders have an increased likelihood of serious clinical consequences and less favourable long-term outcomes, including, for example, risk of hospitalisation [3], medication noncompliance [4], violence [5], overdose [6] and suicide [7]. The most frequently used substances are tobacco, alcohol, cannabis and cocaine and, especially in the US, rates of substance misuse in people with severe mental illness are considerably higher compared with healthy individuals. According to the *Epidemiological Catchment Area* study [8], about half of people suffering from severe mental disorders have a lifetime comorbid substance use disorder. Moreover, the *National Comorbidity Survey* [9] showed that roughly half of respondents who meet criteria for a lifetime substance use disorder also meet criteria for one or more lifetime mental disorder. Studies in different mental health settings show large differences in dual diagnosis rates among people with severe mental illness, ranging between 20 and 65% [10].

In Europe, moderate size evidence on dual diagnosis has been accumulating since the beginning of the 1990s. Wide variations in rates of addictive behaviours among people with severe mental disorders have been found in European countries [10]. According to the *European Schizophrenia Cohort* (EuroSC) study [11], carried out on 1,208 subjects with schizophrenia in France, Germany and the UK, comorbid alcohol and other psychoactive substances rates were lower than those reported in the US, but higher than the general population. The lifetime prevalence rate for comorbid substance use disorder was 35% in the UK, 21% in Germany and 19% in France.

Despite the high prevalence rates and clinical impact, dual diagnosis and its psychopathological and clinical burden remain often underrated and poorly assessed

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in psychiatric settings. In this overview, we summarise both new and old main issues of dual diagnosis, including psychopathological models, symptoms profiles and clinical issues, aiming to define the peculiar features of individuals with co-occurring mental and substance use disorders.

Psychopathological models and aetiological hypotheses of dual diagnosis

The strength of the epidemiological, clinical and biological association between substance use and severe mental disorders has determined a large number of research initiatives aimed at clarifying the nature of this association. However, there are no clear and uniformly accepted definitions of comorbidity, and dual diagnosis has no coherent theoretical framework [12]. Various conceptualisations of *dual diagnosis* have been suggested to assess if comorbid disorders are part of the same clinical syndrome or represent two or more different and independent conditions [13]. Psychiatric nosology has traditionally emphasised the importance of differentiating temporary psychiatric symptoms observed only in the context of intoxication and withdrawal influences, and psychiatric conditions determining full diagnostic syndromes, independently from the comorbid substance use disorder [14 15]. Although the nosological analysis of comorbidity may enhance the generalisability of research findings [16], dual diagnosis represents a complex and heterogeneous entity, and different drugs and alcohol may not necessarily share identical relationships with different mental disorders. The growing and long-term interest in this area might be considered under several points of views. Under an atheoretical point of view, most research has been focused on the analysis of the correlation between addiction and mental disorders, using disease definitions derived from the standardised diagnostic entities of the DSM and postulating a diagnostic independence of two distinct and comorbid pathological conditions. Nevertheless, it should be highlighted that co-occurrence of mental disorders and addictive behaviours complicates psychopathological features and makes nosology more complex. Clinicians should be aware that reductive categorical or one-dimensional approaches heighten the risk to lose the psychopathological meaning of dual diagnosis phenomenon. Dual diagnosis is not a simple *summa* of two clinical entities to *think*, treat and manage separately, but represent a single pathological entity where different psychopathological elements join together, influencing negatively each other. Indeed, if the focus of categorical diagnoses is addressed to identify elements building categories of subjects who fall into pre-established diagnostic criteria, the diagnostic approach for dual diagnosis should be aimed at recognising those dimensions overcoming diagnostic categories in favour of psychopathology [17]. The interpretation of comorbidity needs a comprehensive awareness that dual diagnosis represents a complex phenomenon in which only a multidimensional understating may allow to fully understand the phenomenon. In such context, it is easy to recognise all problems related to artificial separations of dual disorders, not only in terms of diagnosis and treatment, but also of service organisations [1].

Nevertheless, aiming to build upon a common theoretical framework of dual diagnosis, it may also be useful to analyse etiological models, even if they are incomplete. Indeed, an ideal psychiatric nomenclature needs to define syndromes on the basis of established aetiology and pathophysiology [15]. Theories on potential aetiological links have been widely explored during the last 30 years, but the underlying mechanisms of the association between mental and substance use disorders are not entirely clear. Attempting to overcome the "chicken and egg" paradox [18], a number of explanatory models of substance use among people with severe mental disorders have been proposed. Supporting the paradigm that substance use disorders might be the consequence of mental disorders, the "self medication" hypothesis has been proposed [19]. According to this model, substance use disorder would represent the consequence of a severe mental disorder, occurring in a context of self-regulation vulnerability and individual difficulties in controlling subjective emotions, affects, relationships, and self-care [20 21]. This hypothesis suggests that self-medication by alcohol or illicit substance use may have the role of a coping strategy addressed to treat and reduce anxiety, anhedonia, psychotic symptoms, or painful affect states [20 21]. It has been shown that subjects with mental disorders tend to use substances to relieve depressive symptoms, social withdrawal and apathy. As previously reported, substance use for several patients becomes the instrument that allows to avoid falling into the pain of insight, to make sense of life's experiences, or even moving symptoms that are difficult to express otherwise [17]. Drake & Wallach [22] highlighted that, under a phenomenological perspective, experiences with alcohol and illicit substances represent a confused attempt to survive the stress and other consequences of mental illness, including victimisation, lack of social opportunities and hopelessness. Among people with psychotic disorders, the main reasons for self-medication reported by individuals with alcohol or illicit substances use disorders include relieving depression, achieving or maintaining euphoria, improving self-confidence and social abilities [23]. Data from the *National Epidemiologic Survey on Alcohol and Related Conditions* (NESARC) [24] on 34,653 US adults show that those who had used alcohol

or other psychoactive substances to reduce fear, anxiety, or avoidance symptoms had a significant risk of incident alcohol or substance dependence, with adjusted ORs of 2.6 (1.0-6.7) and 5.0 (1.7-14.2), respectively. However, further findings from NESARC [25] did not support the self-medication hypothesis, highlighting that both mood and anxiety disorders might influence the transition from substance use to abuse and/or dependence rather than from abstinence to use.

It has been suggested that patients may use substances to self-medicate adverse effects of antipsychotic drugs, especially akinesia and akathisia [26 27]. This hypothesis is not totally confirmed by research. Indeed, it has been shown that patients with schizophrenia and comorbid substance use disorder have more extrapyramidal effects than non-abusing patients [28]. For example, cocaine use disorder is associated with severity of dyskinesia, parkinsonism and akathisia [28 29].

Furthermore, the self-medication model should imply that people with mental disorders might have similar patterns in both substance selection and psychopathology, but the available evidence does not entirely support this hypothesis. Self-medication can explain some, but not all, of the reasons for high comorbidity rates among individuals who suffer from mental disorders. Substances used by individuals with mental disorders are widely heterogeneous, with no replicable patterns of abuse/dependence, and appear to be related with other factors in addition to self-treatment. Drug selection appears correlated with environmental factors [30] rather than with specific symptoms of mental disorders, e.g. negative symptoms. No significant differences were found across different diagnostic subgroups on severity, since substances of choice and length and patterns of use seem to reflect those found in the general population [31].

Finally, evidence that people with co-occurring substance use disorder have generally worse clinical features at least partly disproves the hypothesis of self-medication. Substances produce a heterogeneous range of effects, but generally exacerbate rather than relieve symptoms of underlying mental diseases [32]. If alcohol or illicit substances are used to increase pleasure, to *get high* and to reduce negative psychotic and anxiety symptoms, increased depressive or positive symptoms have been reported [33 34]. People with co-occurring severe mental and substance use disorders appear clinically and socially impaired, more severely ill and more often hospitalised or homeless [21]. It is still unclear whether these characteristics are causes or consequences of persistent substance abuse.

The unidirectional causality seems inconsistent and is not totally supported by the temporal relationship between the onset of substance use and the occurrence of mental disorders. It has been highlighted, for example, that alcohol or substance use disorders often precede rather than follow the onset of mental disorders. Hambrecth & Hafner [35] have shown heterogeneous temporal links pointing out that alcohol abuse more often followed first psychotic symptoms, whereas substance abuse preceded psychosis in 27.5%, followed it in 37.9%, and emerged within the same period in 34.6% of the cases. Some reports on the temporal relationship between addiction and mental disorders are also available for anxiety disorders. However, mixed results have been reported and, while social phobia has been predominantly identified as a primary disorder preceding substance use [36], the temporality of other anxiety and substance use disorders is less clear.

The second proposed model involves the hypothesis that mental disorders might be the consequence of a chronic substance use [37]. This widely debated association is essentially based on the stress-vulnerability model in which substance use represents the stressor precipitating the onset of mental disorders in vulnerable individuals [16]. Although some studies have underlined the potential link between alcohol, opioid, stimulant use and the occurrence of different mental disorders [34 38], the association between cannabis use and the development of related psychotic disorders has received particular attention. In the last 20 years, an increasing body of research has explored if cannabis might influence, in a dose-dependent manner, the onset of psychotic disorders. Although findings on cannabis and psychosis association need to be interpreted with caution, there is reasonable evidence from prospective studies that regular cannabis use is associated with an increased likelihood of schizophrenia and other psychotic disorders [39]. Use of cannabis has been suggested to confer about a twofold higher individual risk for later schizophrenia and, at the population level, the elimination of cannabis use might reduce the incidence of schizophrenia by approximately 8% [40].

Systematic reviews analysing the link between cannabis and psychotic disorders added evidence about the potential role of cannabis in the pathogenesis of schizophrenia. Moore et al. reviewed 35 studies on the relationship between cannabis use and the occurrence of psychotic or affective mental health outcomes, and found an increased risk of any psychotic outcome in individuals who had ever used cannabis [41]. Results were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently. Preliminary studies [42] have reported an increasing use of novel psychoactive drugs, such as synthetic cannabinoids, especially among young people suffering from mental disorders. Synthetic cannabinoids may also exacerbate psychotic symptoms in vulnerable individuals [43], and the use of these psychoactive drugs could explain otherwise inexplicable new psychotic symptoms, especially

in young people [44]. It is interesting to note that preliminary data [43] show that the occurrence of psychopathology and symptoms, such as hallucinations, delusions, behavioural problems and loss of control, might be more likely among people using synthetic cannabinoids compared with those using natural cannabis.

The phenomenon of *spiceophrenia* [45] has been recently described exploring relevant research, including surveys, toxicology studies and case series. Although a clear causal association cannot be identified, the available evidence suggests that synthetic cannabinoids may induce acute and transient psychoses in vulnerable people or in individuals with prodromal symptoms as well as relapses in subjects with a history of mental disorders. Symptoms related to acute or chronic use of synthetic cannabinoids highly vary in terms of psychopathology, and seem to be characterised by paranoid thoughts/combativeness/irritability, altered perceptions/mental status, thought disorganisation, confusion, agitation/anxiety/panic attacks/restlessness and depressive states with suicidal thoughts [45].

However, although the aetiological role of cannabinoids in chronic psychosis can be supported by some neurobiological models [46 47], cannabis seems to be neither a sufficient nor a necessary condition for the onset of chronic psychotic disorders, appearing as one of the several known and unknown factors that interact each other increasing the individual risk of psychosis [40 48]. The role of cannabis on psychosis may be a good example of the role of the gene/environment interaction in determining vulnerability in psychiatric disorders [48 49].

Furthermore, the association with cannabis does not appear to be specific. Interestingly, it has been found that cannabis use might play a role also in the occurrence of mental disorders other than psychoses. Preliminary data found that cannabis use might worsen the occurrence of manic symptoms in people with bipolar disorder and might also have an effect on the incidence of manic symptoms [50]. On the other hand, Lev-Ran et al. [51] highlighted that cannabis users have a significantly higher likelihood to develop depression compared with non-users (odds ratio [OR] = 1.17; 95% confidence interval [95% CI]: 1.05-1.30), and this association is stronger among heavy cannabis users (OR = 1.62; 95% CI: 1.21-2.16).

It should be taken into account also the potential role of tobacco that is frequently used in association with cannabis. Rates of smoking among people with psychotic disorders are notoriously high [52], with an estimated prevalence of almost 60% in people with a first episode of psychosis [53]. Even for tobacco, the reasons why people with psychosis are more likely to smoke compared with the general population are still unclear. A recently published meta-analysis [54] reported findings for tobacco similar to cannabis. From prospective studies, an overall relative risk of new psychotic disorders in daily smokers *vs* non-smokers of 2.18 has been found (95% CI: 1.23-3.85). Furthermore, daily smokers developed psychotic illness at an earlier age than non-smokers (weighted mean difference [WMD] = -1.04 years; 95% CI: -1.82 to -0.26). Therefore, the association between smoking and psychosis deserves further examination.

The third model hypothesises that dual diagnosis might be due to shared risk factors common to both mental disorders and addictive behaviours.

Accumulating evidence shows that genetics and gene/environment interaction may represent the common underlying factors between these two disorders [49]. It seems that there may be an overlap between genes identified in schizophrenia and those found in addictive behaviours, i.e., genes involved in neuroplasticity and brain development and genes that modulate the activity of dopamine and other catecholamines [49].

The involvement of brain dopaminergic pathways is likely to be a shared characteristic of dual diagnosis. The mesolimbic dopamine pathway has been implicated not only in the rewarding mechanism implicated in the substance use disorders, but also in the occurrence of positive symptoms in schizophrenia. On the other hand, the mesocortical dopamine pathway is a contributor of the presence of negative symptoms in schizophrenia and has been involved in the neuroadaptation resulting from repeated substance exposures [49].

Recently, a 'cannabinoid hypothesis', other than the 'dopamine hypothesis', has been suggested [55], although findings supporting endocannabinoid system dysfunction in schizophrenia are not entirely consistent across studies. It seems that alterations affecting the cannabinoid CNR1 gene lead to genetic predisposition for schizophrenia [56]. On the other hand, alterations in the endocannabinoid system, such as an increased density of cannabinoid CB1 receptor binding in corticolimbic regions and increased levels of cerebrospinal fluid endocannabinoid anandamide, may contribute to the pathogenesis of schizophrenia [55 56].

Mental and substance use disorders may also share dysfunctional environmental factors, including a disruptive family environment and parental abuse or neglect [57]. Especially among women, a childhood traumatic event might be at least partially responsible for the association between anxiety and alcohol use disorders [58]. Other mediators of the relationship between mental and substance use disorders might be represented by specific personality traits, including sensation-seeking, social anhedonia and impulsivity. In particular, a relatively recent study [59] highlighted that sensation-seeking and social anhedonia are prominent in people with substance use disorders

and schizophrenia, respectively, whereas impulsivity is high in people with comorbid disorders.
Impulsivity, i.e., "a predisposition toward rapid, unplanned reactions to internal or external stimuli regardless of negative consequences" [60] may represent a major common substrate of dual diagnosis. According to the reward-delay or delay discounting model, preference for a small immediate reward over a larger delayed one and an exaggeration of the normal hyperbolic loss in value of a future reward with increased time, characterises vulnerability of people who suffer from both mental and substance use disorders. Impulsivity negatively influences decision making and is frequent in people with alcohol and substance use disorders as well as among individuals who suffer from psychotic, bipolar, stress-related and cluster B personality disorders [7 61 62]. Impulsivity may also be the substrate for the high rates of suicide [7] and violence [63] found in people with dual diagnosis.

Psychopathological features of dual diagnosis

The onset of mental health problems among people with substance use disorders is typically earlier than among those without comorbid addictive behaviours. Meta-analytic data have established the extent to which use of tobacco, cannabis, alcohol and other psychoactive substances affect the age of psychosis onset. It has been highlighted that daily smokers develop psychotic disorders about one year before than non-smokers [52]. Other findings provide evidence for a relationship between cannabis use and earlier onset of psychosis, showing that the onset among cannabis users is about two years earlier than among nonusers [64]. A meta-analytic replication [65] suggests that the association between cannabis use and earlier onset of psychosis is consistent and not influenced by other potentially confounding factors, such as tobacco smoking. On the other hand, alcohol use is not associated with a significantly earlier age at onset of disease [64].
Similar findings have been reported in studies exploring other mental and substance use disorders. For example, the *Sequenced Treatment Alternatives to Relieve Depression* study [66] pointed out an age at onset of the first depressive episode significantly lower among those with comorbid substance use disorder (23.7 vs. 25.7 years).
Furthermore, people with dual diagnosis are more often males. Men with severe mental disorders have higher rates of comorbid substance use than women, while clinical outcomes of both mental and substance use disorders among women might be characterised by poorer prognosis. Although dually diagnosed women have more social contacts and fewer legal problems, they have greater problems with victimisation and medical illness than men [67]. Male patients with dual diagnosis are more likely to be admitted for schizophrenia and to use substances other than alcohol, whereas female patients are more likely to be admitted for affective disorders and to have experienced emotional, physical, or sexual abuse or having been crime victims [68 69].
Individuals with dual diagnosis generally have more severe clinical features than those without comorbid disorders. However, findings are consistently heterogeneous according to type of mental or substance use disorders involved, as well as temporal relationship between psychiatric and addictive disorders [70]. Some research comparing symptoms in people with dual diagnosis with those in non-abusing individuals is available, especially from studies analysing subjects suffering from schizophrenia and other psychotic disorders. Differences between subjects with schizophrenia, using and non-using alcohol or substances, seem not striking, but some interesting symptom patterns have been found [71]. High levels of derealisation, depersonalisation, ambivalence, hopelessness and sudden delusional ideas more often characterise clinical presentations of people with co-occurring schizophrenia and substance use disorder. Psychopathological differences seem mainly related to involved substances, potentially inducing intense hallucinations and psychotic symptoms rather than to a persisting or predisposing clinical pattern. The body of the literature suggests high levels of positive symptoms in dual diagnosis patients than in non-addicted individuals with severe mental disorders.
A meta-analytic comparison [72] based on nine studies (accounting for 725 individuals) tested the hypothesis that people with schizophrenia and comorbid substance use disorder have more positive and less negative symptoms than their non-comorbid counterparts. Although total *Positive and Negative Syndrome Scale* (PANSS) scores did not differ (77.8 ± 14.0 *vs* 79.2±17.0), the meta-analysis highlighted that there were markedly higher PANSS-positive (WMD = 2.01; 95% CI: 1.19 to 2.84), and lower PANSS-negative scores (WMD = -1.86; 95% CI: -2.72 to -1.00) among subjects with comorbid substance use disorders. A similar meta-analysis [73] showed that patients with co-occurring schizophrenia and substance use disorders experience fewer negative symptoms than abstinent individuals. These results suggest either that substance abuse relieves the negative symptoms of schizophrenia or that individuals with fewer negative symptoms would be more prone to substance use disorders. Nevertheless, the available meta-analytic data [74] highlight a small, positive and significant trend for depressive symptoms among dual-diagnosis patients as compared with single-diagnosis individuals, especially for studies using the *Hamilton Depression Rating Scale* to assess symptoms.
Evidence is available also for mental disorders other than schizophrenia. Main differences for dually diag-

nosed individuals with major affective disorders involve higher levels of hypersomnia and anxious mood in people with major depressive disorders [66], and more anxiety and stress-related symptoms in people with bipolar disorders [75].

Symptom patterns of bipolar disorders strictly depend on the substance misused, with cannabis use selectively and strongly preceding and coinciding with mania/hypomania, and alcohol use preceding or coinciding with depressive episodes [76 77].

Moreover, cognitive functioning has been widely explored in people with severe mental disorders. Although use of drugs is associated with impairment in cognitive function in healthy people, the potential role of substance use disorders on cognition of people with mental disorders remains unclear and produces conflicting results, probably related to methodological limitations [78]. It has been shown that some people with comorbid substance use might not have poorer social and cognitive functioning than their non-comorbid counterparts [79]. A matched, cross-sectional study [80] comparing social and cognitive functioning of subjects with psychotic disorders did not find any differences between abusing and non-abusing subjects. A comparative study [81] exploring whether response inhibition and cognitive flexibility are differentially impaired among patients suffering from schizophrenia with or without comorbid substance use disorder highlighted that non-addicted individuals show the most pronounced executive function impairments. A further exploration [82] indicated that schizophrenia is characterised by severe working memory and multi-tasking deficits. However, deficits on performance are not exacerbated by comorbid substance use disorder.

Research on dual diagnosis has highlighted the high risk of subjects with co-occurring disorders in terms of long-term prognosis and treatment response, independently of its specific clinical manifestations. In particular, several studies have reported lower medication compliance in comorbid patients. Severity of symptoms expressed by subjects with dual diagnosis can be due not only to the direct effects of substances on psychiatric symptoms, but also to medication noncompliance [16]. Poor compliance with treatment regimens in comorbid people seems to be associated with more negative subjective or dysphoric responses [83]. It has been reported that patients with dual diagnosis and low treatment compliance are significantly more likely to have comorbid personality disorders, lower global assessment of functioning scores, more medication side effects, lower self-efficacy for drug avoidance and poorer social support than those without treatment compliance problems [84 85]. However, level of insight probably remains the most important factor in determining whether a patient is regularly compliant, after controlling for comorbid substance misuse and other confounding variables [83]. It seems likely that a better understanding of reasons for noncompliance might be helpful in quantifying the amount of noncompliance mediated by severe symptoms and that attributable just to comorbid substance use [16]. Indeed, when comorbid patients are adequately treated for their psychiatric illness, there is a considerable improvement in symptoms, even if substance use remains unchanged [16].

As a cumulative effect of substances, mental disorders and low treatment compliance, people with dual diagnosis have a greater risk to commit suicide. Evidence has shown that people with both mental and substance use disorders have higher rates of both lifetime suicide ideation and suicide attempts. Severity of psychopathology, higher hopelessness and impulsivity, as well as temperament profile, including dysthymic/cyclothymic/anxiety and irritability traits, all may represent important clinical correlates [86]. Co-occurring alcohol and substance use disorders might be related to poor coping skills and social adversities, which are also risk factors for suicidal behaviour[7]. It has been established that the negative effects related to alcohol consumption, bad experiences from drug use, as well as delusions or hallucinations during depressive symptoms, could all represent independent risk factors for suicide attempts in patients with alcohol use disorders and a history of depressive symptoms [87]. Furthermore, impulsivity represents an important feature of people with dual diagnosis potentially complicating course and treatment of both substance use and mental disorders [88 89]. Addiction could play a mediating role on the effect of impulsivity on suicide attempts, fostering aggression and hostility that increase the risk of acting on suicidal thoughts. It is also possible that both suicidal behaviours and alcohol and drug use represent maladaptive strategies to manage negative symptoms and depressive states. Substance use disorders can increase the risk of mood instability – an important factor associated with suicidal thoughts or attempts – among people with bipolar disorders, including the susceptibility to switch from depression to manic, hypomanic, or mixed states [7]. The combination of comorbid disorders, negative environmental effects and a more severe course is consistent with the wide range of factors associated with attempted suicide across a number of severe mental disorders [7].

Moreover, conceptual models hypothesise that individuals with severe mental disorders are at higher risk of committing violent acts, representing itself an established risk factor for violent crimes [90]. However, rigorous research found that the association between severe mental disorders and violent crime is minimal unless the individual is also diagnosed as having a substance use disorder [5]. Meta-analytic data [91] found that the risk of violence is increased in both

individuals with psychosis and substance use disorder (OR = 8.9; 95% CI: 5.4-14.7) than in general population controls, whereas a consistently lower association was found in non-comorbid people with psychoses (OR = 2.1; 95% CI: 1.7-2.7). Furthermore, risk estimates of violence in individuals with psychosis and co-occurring substance use disorders are similar to those in individuals with substance use disorders, but without psychosis. Therefore, psychoses did not appear to add any additional increase to the risk of violence compared with that due to substance use alone [91]. It is possible that psychotic disorders lead to substance use disorders, which in turn increases the risk of violent behaviours, but limited support for this interpretation has been found. An alternative model is that severe mental disorders and violent behaviours co-occur since both are related to common personality traits such as irritability and inadequate coping with anger or stress [5]. Finally, a shared genetic susceptibility to addiction, schizophrenia and violent crime has been suggested.

Violence and serious aggression often precede diagnosis of schizophrenia, even after controlling for preadolescent psychotic symptoms [92 93]. It has been demonstrated that conviction of violence in late adolescence is associated with a fourfold higher risk for a future diagnosis of schizophrenia, suggesting a role of violent behaviour as a part of the prodromal psychosis syndrome. Childhood psychotic symptoms, as well as physical aggression, represent strong risk factors for violence in adults with psychotic disorders [93]. A role of childhood conduct problems has also been hypothesised. Prospective studies have pointed out that childhood conduct problems other than substance abuse represent important predictors of violence in people with schizophrenia [5].

Conclusions

During the past three decades, growing attention has been dedicated to the dual diagnosis phenomenon. The comorbidity between severe mental disorders and alcohol or substance use disorders represents a common and serious clinical challenge, characterised by high prevalence worldwide. The co-occurrence of these disorders complicates treatment, management and prognosis of both disorders, but it remains often unrecognised and undertreated. Mental health and addiction professionals should accurately assess and evaluate this comorbidity, although related aetiological links, temporal relationships and psychopathological issues are still not entirely clear and, probably, heterogeneous and multifactorial. In many countries, the challenges are exacerbated by the mental and addiction disorders being managed in parallel delivery systems staffed by providers with different knowledge base, skills and attitudes. Attempts at integrating service delivery are ongoing, but implementation of common treatment guidelines is not easy.

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Novel psychoactive substances and induced phenomena in psychopathology: the lysergic psychoma

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Summary

Novel psychoactive substances (NPS) are defined as new narcotic/psychotropic drugs that are not controlled by the United Nations' Conventions on Narcotic Drugs (1961) or Psychotropic Substances (1971), but which may pose a comparable public health threat. The use of NPS is an emerging issue that will challenge psychopathology for years to come. The knowledge of health professionals about the acute/chronic physical and psychopathological manifestations associated with NPS intake is still scarce and fragmentary.

The lysergic psychoma is a construct that may be pivotal in the understanding of phenomena induced by NPS in general, not only by lysergic hallucinogens. The model of hexogen psychosis developed by Karl Bonhoeffer may help to understand what happens during and after the intake of these substances.

More clinical studies are needed to clarify these aspects and the importance of the hexogen model, not only in the perspective of toxic psychosis. This latter may represent a heuristic model that can help to better understand the psychotic prozess *as a whole.*

Key words

Novel Psychoactive Substances • Hallucinogens • Psychosis • Lysergic psychoma • Induced phenomena

Novel psychoactive substances: main groups and characteristics

Novel psychoactive substances (NPS) are defined as new narcotic/psychotropic drugs that are not controlled by the United Nations' Conventions on Narcotic Drugs (1961) or Psychotropic Substances (1971), but which may pose a comparable public health threat [1]. The adjective "novel" does not necessarily mean that these drugs have been synthesised in recent times; it mainly refers to substances that have lately gained popularity/availability in the recreational drugs market, becoming a reason of potential health concern. Many NPS are research chemicals, or even discarded products from pharmacological research that have been rediscovered and/or slightly modified to obtain effects similar to those of known illicit substances [2]. In other words, NPS do not necessarily constitute new molecules/inventions. Moreover, NPS are often manufactured in unofficial laboratories and without any control on the hygienic standards of the productive process, raising further concerns for the presence of contaminating agents such as heavy metals or other licit/illicit drugs [3]. Over the past 10 years, novel psychoactive substances have flooded the global market, and are advertised in head shops and over the Internet as 'safer' and 'legal' alternatives to illicit drugs. NPS are commercialised with marketing strategies specifically designed to attract customers, especially young people: colourful packaging, fun brand names, discounts and special offers are commonly used by NPS retailers [4].

NPS misuse has been identified in 94 countries/territories; the number of European young people who declare to have ingested NPS at least once in their life has risen from 5% to 8% between 2011 and 2014 [5]. Compared to 2011, the countries where the consumption of new substances has increased the most are Spain (+8%), France (+7%) and Slovakia (+7%). So far, information on the short- and long-term effects of NPS is minimal or inaccurate, and what we are currently witnessing is that they can be just as harmful and addictive as illegal drugs such as cocaine, ecstasy and ketamine. Overall, NPS belong to a range of six categories (see Table I):

- synthetic cannabimimetics ('spice', 'K2' drugs);
- synthetic cathinones ('meow meow', 'bath salts' and others);
- latest generation phenethylamines/MDMA-like drugs, such as 'fly' drugs, NBOMe derivatives, DMAA and a range of indanes;

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TABLE I.
NPS: typologies and psychopathological consequences.

NPS category	Most popular compounds	Overall psychopathological consequences
Synthetic cannabimimetics	"Spice"; "K2"; "Bonzai"; "Black mamba"; "Psyclone" etc.; including: AM-2201; AM-2233; AKB-48F; 5F-AB-PINACA; 5F-AKB-48; 5F-AMB; 5F-MN-18; 5F-PB22; 5F-SDB-005; 5F-SDB-006; AB-CHIMINACA; AB-FUBINACA; AB-PINACA; BB-22; EG-018; FAB-144; FDU-PB22; FUB-PB22; NM-2201; PB-22; THJ-018; THJ-2201 etc.	• Agitation/anxiety • Visual/auditory hallucinations • Altered mood and behaviour agitation; dysphoria; manic-like symptoms; and relapse of pre-existing bipolar disorders • Occurrence of florid/acute transient psychosis; relapse/worsening of a pre-existing psychosis; persisting psychotic disorders/'Spiceophrenia' • Suicidal ideation • Possible serotonin syndrome
Synthetic cathinones	Mephedrone/'meow; methedrone; methylone; 3-MeOMC; 3-MMC; 4-BMC; 4-MEC; 4-MeO-a-PVP; 4-MeO-PBP; 4-MeO-PV9; 4-MPD; 4F-PV8; 4F-PV9; 4F-PVP; a-PBT; a-PHP; a-PVT; dibutylone; DL-4662; ethylone; MDPPP; NEB; pentedrone; PV-8 etc.	• Increased alertness/euphoria hallucinations/agitation/aggression affective disturbances • Paranoid ideation possibly observed in chronic users • Decreased DA transporters on PET scans, suggesting the potential risk for long-term neuropsychiatric problems
Psychedelic phenethylamines *(novel derivatives)*	Fluoroamphetamine, PMA, 2C-T, 2C-B; 'Bromodragonfly'; NBOMes; indanes; benzofurans (5; 6-APB/APDB; 5-EAPB; 5-MAPB); 'BenzoFury'; etc.	• Euphoria/agitation • Psychosis/hallucinations • Possible serotonin syndrome
Tryptamines *(novel derivatives)*	5-Meo-DALT (N,N-diallyl-5-methoxytryptamine); AMT (α -methyltryptamine/'IT-90'; 5-Meo-aMT (5-methoxy-α-methyltryptamine); 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine), 5-MeO-DPT (5-methoxy-N,N-dipropyltryptamine); bufotenin; 5-Meo-αMT; 5-MeO-DMT; 5-IT	• Common visual hallucinations • Possible auditory hallucinations • Altered sensory perception/body image distortion/depersonalisation/marked mood lability/euphoria/ relaxation/entactogenic properties/anxiety/panic disorder • Possible serotonin syndrome
Piperazines	BZP; mCPP; TFMPP	• Increased energy/irritability/anxiety/ paranoid ideation • Hallucinations at high dosages
Others	Plants: e.g. Salvia divinorum; Kanna/ Sceletium tortuosum; Mytragina speciosa/ Kratom. Pharmaceuticals: e.g. gabapentinoids, phenazepam Performance and Image Enhancing Drugs (PIEDS): e.g., cognitive enhancers	• *Salvia divinorum*: euphoria/reduction of tension/libido enhancement/appetite suppression • *Kanna*: empathogen; appetite suppressant; euphoria; hypertension; anxiety/irritability; perceptual/visual disturbances • *Kratom*: opiate-like sedation at higher dosages; possible perceptual/visual disturbances • *Gabapentinoids' high dosages*: euphoria/ improved sociability/sedation/'opiate buzz'/psychedelic effects/entactogenic feelings/dissociation • *Benzodiazepines*: sedation; possible paradoxical effects (anxiety/irritability) • *Cognitive enhancers*: possible hallucinogenics/mood altering effects

- latest generation tryptamine derivatives such as 5-Meo-DALT, AMT;
- piperazines, e.g. BZP;
- other substances, such as herbs/plants (e.g., *Salvia divinorum, Mytragina speciosa/kratom*); medicinal products, including a range of opiates/opioids, gabapentinoids, novel benzodiazepines/sedatives, stimulants and antiparkinsonians/anticholinergics; performance- and image-enhancing drugs, such as super-strength caffeine tablets, and cognitive enhancers.

Users are typically attracted by the intense psychoactive effects of these substances, and by the likely lack of detection in routine drug screenings. Indeed, these drugs act on a range of neurotransmitter pathways/receptors whose imbalance has been associated with psychopathological conditions, including dopamine, cannabinoid CB1, GABA-A/B, 5-HT2A, glutamate and k opioid receptors.

Synthetic cannabimimetics (SCs) are a few hundred molecules designed to functionally resemble the effects of the main active compound of natural cannabis, Δ9-tetrahydrocannabinol (THC). SCs possess an extremely higher cannabinoid receptor binding affinity level than THC itself, with a significantly more intense dose-response efficacy. SCs mixtures are commonly sprayed over dried herbal material and smoked. According to data provided by the *Substance Abuse and Mental Health Services Administration*, in 2010 11,406 accesses to the emergency department in the US were due to synthetic cannabinoid consumption; the number of accesses has more than doubled in 2011 (28,531). Of these, 75% of emergencies involved young or very young patients, aged between 12 and 29 years old, predominantly males (79%) [6]. The most commonly reported adverse effects are tachycardia, drowsiness/lethargy, agitation/irritability, vomiting, hallucinations/delusions, nausea, confusion, hypertension, chest pain and dizziness. Patients also reported disorganised behaviour, mood alterations, intense suicidal ideation and/or behaviour [7]. SC intake has also been associated with the occurrence of florid/acute transient psychosis, relapse/worsening of a pre-existing psychosis and persisting psychotic disorders, the so-called "spiceophrenia" [8].

Synthetic cathinones (SCath) are central nervous system stimulants, structurally similar to amphetamines/catecholamines and derived from the active compound cathinone, present in the plant Catha Edulis (known as Khat or Qat). The main cathinone derivatives are the semi-synthetic methcathinone and the synthetic compounds mephedrone, methylone and methylenedioxypyrovalerone (MDPV). Typically, SCath are snorted, ingested orally ("bombed", namely swallowed after being wrapped in cigarette paper) or injected. The main effects of synthetic cathinones on CNS are mainly due to their ability to act on monoamine reuptake, determining an increase of dopamine, serotonin and noradrenaline at a synaptic level [9]. More than half of mephedrone users experience both physical and psychological unwanted effects, including nausea, vomiting, flushing, sweating, tremors, headache, blurred vision, restlessness and anxiety [10]. Other referred serious adverse effects of mephedrone include hyperthermia, rhabdomyolysis, renal failure, seizures and arrhythmias. Chronic users also report mood disturbances and paranoid ideation [11]. Synthetic cathinones appear to be peculiarly involved, more than other NPS, in the development of both self- and other-oriented violent behaviours: a number of case reports in human users of cathinone drugs highlighted that they tend to produce increased aggression, including suicide [12].

Other NPS include piperazines, whose effects are similar to those of amphetamine but slightly less intense; psychedelic phenethylamines/MDMA-like drugs (2C drugs; Fly drugs), which enhance mood, increase energy and talkativeness and cause perceptual alterations; tryptamines, whose main effects are due to their agonist activities on 5-HT2A receptors and serotonin transporter inhibition, and consist in visual hallucinations, altered perceptions, body image distortion, derealisation/depersonalisation, marked mood lability; natural (Ayahuasca, Salvia divinorum) and pharmaceutical products (e.g. gabapentinoids, phenazepam), which encompass a wide range of substance-specific desired and untoward effects.

NPS intake and psychopathological issues

The recent development of a huge number of NPS, combined with the ability of the Internet to spread information quickly, represents a global and unprecedented challenge for both public and mental health. The knowledge of health professionals on the acute/chronic physical and psychopathological manifestations associated with NPS intake is still scarce and fragmentary. Moreover, a further alarming trend may derive from misuse of novel psychoactive substances in young psychiatric patients: NPS may reduce the adherence to therapeutic plans and the efficacy of treatments for psychiatric disorders, and may also worsen the symptoms of a pre-existing pathology [13].

NPS may precipitate the imbalance of a wide range of neurotransmitters/pathways/receptors; e.g. dopamine/DA (mostly associated with the intake of psychedelic phenethylamines/synthetic cathinones); CB-1R activation (synthetic cannabimimetics); 5-HT2A receptor activation (tryptamine derivatives/hallucinogenic plants); antagonist activities at both NMDA and mGlu2/3 receptors (PCP-like derivatives); and k opioid receptors' activation (Salvia divinorum) (Table I). With regards to the most frequently observed clinical features related to NPS consumption,

anxiety, dysphoria, increased aggression, mood fluctuations and perceptual/thought disturbances are to be mentioned. As previously stated, a number of recent studies have highlighted a close relation between synthetic cannabimimetic use and the onset of schizophrenic-like symptoms [8]. Scientific research has recently focused on induced psychotic experiences in the past few years. The study by Caton et al. aimed at identifying key demographic, family and clinical differences in substance-induced psychosis and primary psychotic disorders in 400 participants with at least 1 psychotic symptom, use of alcohol and/or other drugs in the previous 30 days and no psychiatric inpatient history before the previous 6 months. Of this sample, 44% was diagnosed with a substance-induced psychosis, while 56% with a primary psychosis. The patients included in the substance-induced psychosis group had more common visual hallucinations, a higher prevalence of suicidal thoughts during the previous year, more common violent behaviour, more frequent family history of substance abuse and higher levels of insight [14]. Other studies have described psychotic states induced by methamphetamine consumption (methamphetamine-associated psychosis, MAP), characterised by paranoid delusions and visual/auditory hallucinations, with an enhanced vulnerability to relapse of psychosis and very long duration of vulnerability to relapse [15]. Paranoia appears to occur increasingly rapidly in the course of a session of methamphetamine use. Moreover, the severity of methamphetamine dependence and antisocial personality disorder appear to be predictive of methamphetamine-induced psychosis [16].

The number of subjects not recovering from the induced episodes is relevant, opening the question about the relationship between substance abuse, particularly if continuous and at high dosages, and development of a full psychosis. With regards to this, the model of hexogen psychosis and its toxic subtype, frequently reported as lysergic psychoma, may be helpful to shed light on the issue.

The lysergic psychoma

The lysergic psychoma is a construct that may be pivotal in the understanding of phenomena induced by NPS in general, not only by lysergic hallucinogens. This term, which was used for the first time by Cargnello and Callieri in 1963, has its roots in the definition made by Hellpach and, most of all, in the Karl Bonhoeffer's hexogen model. The term "lysergic psychoma" describes a syndrome characterised by a clear egodystonic experience in which the subject perceives the presence of a "foreign body" in his own mind. The thinking Ego can feel and observe it as an uncommon experience, out of control, enriched by hallucinations (mainly visual and kinesthetic), delusional perceptions and, in some cases, structured but confined delusional thoughts. The Ego is still aware and in charge of its role, and usually tries to stem and contain the overflowing psychoma.

This experience is usually self-limiting, in line with what is considered an induced phenomenon, and considering the transient pharmacodynamic effects exerted by the substance. However, taking into account its repetitive nature, the high dosages and long-lasting pharmacokinetic properties of novel compounds, a new scenario may be hypothesised. If the thinking Ego has to face a stable and repetitive abnormal experience, its resilience and its capacity to contain it might be overcome. If unusual thoughts or deviant perceptions become permanent, the capacity to deflate them is reduced to be more and more inadequate. The thinking Ego may not able to counteract the psychoma anymore, and the latter can invade the functioning part of one's mind, becoming fully pervasive. This could be the beginning of a psychotic experience, an epidemic diffusion inside the brain.

Karl Bonhoeffer and the hexogen model of psychosis

Karl Bonhoeffer included the lysergic psychoma among the models of hexogen psychosis in which an external *noxa* may determine and directly influence the development of a full psychosis. Bonhoeffer firstly described this phenomenon while working in Breslau with alcoholic patients, under the supervision of Wernicke [17]. His aim was to identify the base of a functional dysfunction, a hexogen complex that could interact with an endogenous background and then produce a full psychosis.

Bonhoeffer subsequently moved to the University of Berlin, where he fully developed the concept of a hexogen reaction, rather uniform, determined by an external *noxa*, which could be toxic, infective, traumatic or degenerative. The core characteristic he considered was impaired consciousness, ranging from confusion and dream-like experiences to delirium and stupor [18]. Bonhoeffer's hexogen model was generated in a dialectic relationship with Bleuler's endogenous model, in the same period of Bleuler's first use of the term schizophrenia [19]. Schizophrenia has in itself the idea of *prozess*, including the aspects of progression, worsening and cognitive decline deeply influenced by Kraeplin. The concept of *prozess* was subsequently related to the emergence of the proposals of sterilisation and euthanasia for psychiatric patients. The hexogen model was not necessarily to be considered negative and progressive, and this is one of the reasons for its misfortune. In 1938, Bonhoeffer did not adhere to the euthanasic approach for psychotic patients promoted

by the Nazi Party. His hexogen model did not fit with the concept of a progressive pathway towards deterioration and social uselessness: his school was therefore dismissed after 1938 when he left the University of Berlin in favour of Max de Crinis.
The exogenous model of psychosis was never developed in greater detail, while the endogenous one influenced all German psychopathology and still constitutes the basis of the main diagnostic approaches. The lack of attention paid to the school of Bonhoeffer, which was not consistent with the myth of chronicity and its fatal progression, was anyhow extremely negligent, and his reflections deserve a better understanding, not only from the perspective of toxic experiences. The exogenous model moved from Germany and found more interest in France, UK, Scandinavia and Italy. The endogenous model and the Kraepelinian approach remained, however, the official model in Germany, and obtained the role of the main theoretical approach for psychosis until now.

Morselli and the lysergic psychotic experience

In Heidelberg, in 1927, Kurt Beringer, a pupil of Bonhoeffer, developed the idea of psychoma in relation to mescaline and other lysergic drugs [20]. In Italy, Giovanni Enrico Morselli in 1932 ingested mescaline and reported its effects in a number of essays, in which the hexogen model of psychoma was fully explained in relation to a toxic phenomenon [21]. Morselli also described the clinical effects induced by LSD on a sample of volunteers, including himself. He reported a long-lasting syndrome, characterised by visual hallucinations, delusional perceptions and paranoid thinking [22]. This experience was compared to schizophrenia, with the altered perceptive experience as the main link [23-25].

The lysergic psychoma: typologies and characteristics

The lysergic psychoma is an exogenous clinical expression that almost all NPS users may undergo, regardless of the specific chemical class of the substance. Of course, the pharmacodynamics of the drug taken is responsible for the specificity of the possible abnormal induced phenomena.
Substances acting predominantly on serotonergic pathways are most commonly implicated in the development of visual hallucinations with vivid colours, frequently associated with intense emotional experiences, either positive or negative. In order of frequency, the other possible disordered perceptions are kinesthetic and tactile. The presence of auditory, olfactory and gustatory hallucinations is uncommon. Paranoid delusions, particularly with religious content, are possible, but full-blown systematic delusions are rare. A mood alteration towards hypomanic states may be reported, although suicidal thoughts and depression states may occur as well.
Substances mainly acting on dopaminergic pathways are primarily associated with paranoid thought and auditory hallucinations. Delusions of reference, persecution, grandeur and jealousy, as well as hypomanic states, are frequently reported. Aggressiveness and irritability are common, often with dysphoria, anxiety and panic episodes.
Substances mainly acting on glutamatergic pathways usually determine dissociative reactions, such as derealisation and somatopsychic depersonalisation. Visual abnormal perception may be reported, mainly in the form of distortions and illusions. Bodily and kinesthetic hallucinations are frequent, as the occurrence of near-death experiences. Less common are auditory, olfactory and gustatory hallucinations. Delusions with somatic themes are frequent: Ekbow, Capgras and Cotard syndromes have been reported, as well as episodes of demoniac possession and vexation. Psychotic negative symptoms are common. Mood is always flat, with affective blunting, anhedonia and a general sense of anaesthesia and detachment from surrounding environment is frequent. Irritability and aggressiveness may be noted.
These phenomena (serotonergic, dopaminergic and glutamatergic psychoma) cannot be considered as different syndromes, given the frequent overlap of symptoms among them. This is due to the fact that some NPS exert their potential on different pathways, and also because the possibility of polyabuse is the norm rather than the exception. However, the ability to differentiate and characterise clinical presentation may be useful to plan an appropriate therapeutic approach.
With regards to clinical management, the dopaminergic psychoma is the one most frequently reported as long-lasting and with the worse prognosis, as described for shaboo and methamphetamine users in south-eastern Asia. Methamphetamine-induced psychosis is, in fact, a severe form of paranoid schizophrenia, in which the psychoma has overflowed well beyond its limits.

Conclusions

The use of NPS is an emerging issue that will challenge psychopathology for years to come. The onset of psychiatric symptoms after the use of these potent and highly rewarding drugs appears to be the norm, especially in the long term. These episodes, sometimes with clear psychotic features, are often reversible; however, when the use is frequent, persistent, and at high dosages, the onset of full and long-lasting disorders is commonly observed. The model of hexogen psychosis developed by

Karl Bonhoeffer may help to understand what happens during and after the intake of these substances. A foreign body perceived in the mind of the subject, the so-called lysergic psychoma, may be an experience in which the thinking Ego is still able to match and contain the abnormal part. However, when the psychoma is enduring, the Ego resilience may be overcome, opening the doors to a full psychotic experience. More clinical studies are needed to clarify these aspects and the importance of the hexogen model, not only in the perspective of toxic psychosis. This latter may represent a heuristic model that can help to better understand the psychotic *prozess* as a whole.

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Internet-related psychopathology: clinical phenotypes and perspectives in an evolving field

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Summary

Having become an integral part of everyday life, it is not surprising that the Internet has also given birth to a wide range of problematic and, in some cases, pathological behaviours. Under the vague term "Problematic Internet Use" (PIU), many different forms of harmful Internet use are included. A thorough assessment of the most widely reported forms of PIU can help clinicians to recognise core symptom dimensions. Psychopathological elements reminiscent of impulse control, obsessive-compulsive spectrum and substance use disorders have been reported in Internet addicts, with the presence of psychiatric comorbidity representing the rule rather than the exception. Ultimately, Internet addicts can experience significant functional impairment, often reporting negative impact on the family, work and school performances, and legal difficulties. While diagnostic criteria are still investigational, and epidemiologic and treatment studies remain necessary, herein we will provide an overview of the main psychopathological characteristics, clinical phenotypes and scientific advances on PIU.

Key words

Problematic Internet use • Internet addiction • Behavioral addiction • Impulse control disorder

Introduction

The Internet now represents an integral, almost obligatory, part of everyday life: most people communicate, listen to music, shop, read the news, work and learn online or on social networks, often with the help of other digital tools. When, in 1837, the British mathematician Charles Babbage revealed to the world his "Analytical Engine", the first prototype for a mechanical programmable calculator, he probably did not realise how far the human-machine interaction would evolve. Indeed, by the end of the 20th century, the downstream effects of his invention had contributed to a dramatic and likely irreversible change in human life. Although our species has always attempted to produce technology to help meet needs and control the environment, the degree of change since the introduction of personal computers and digital communications is unprecedented, in part due to the "bidirectional" relationship between us and these tools: humans created computers, and computers, in turn, are reshaping humans.

Many sociologists, psychologists, information technology experts and anthropologists have spoken of a "digital revolution" occurring in the last two decades of the last century [1], and compared it to two prior technology-enabled revolutions: mechanisation and electricity in the 19th century and mass production in the early 20th century [2]. Indeed, some have proposed that the abrupt changes taking place in how we utilise information technology at the beginning of the 21st century may point to a second digital revolution [3]. While the first may have been characterised by mass "digitisation" (i.e., the conversion of communication media into a digital format), the second is being described as mass "atomisation" (i.e., the deep penetrance of digital content into people's lives [4], or "virtualism", with "described as the disappearance of any boundary between the physical and virtual worlds [5]. Such developments have rapidly exposed us to an unprecedented volume of information and to novel ways of interacting, seeing and presenting oneself. The result is new personality traits that are incorporated and nurtured online, as well as modifications to how we read, write, remember and process information [5].

Since, among the medical disciplines, psychiatry is the most attuned to social and cultural changes, it is not surprising that mental health professionals, already in the early 1990s, warned about the addictive properties of the Internet, later defining the "typical profile" as a socially-isolated male teenager with poor self-confidence, whose main activity is related to his computer use and internet access [6 7]. The landscape has greatly changed since then,

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as each successive generation has become more familiar with, and reliant upon, the Internet, resulting in less typicality in the problematic Internet user's profile and in problematic online behaviour. Consequently, different psychiatric disorders related to the use of new digital tools have been proposed. The aim of the present paper is to review Internet-related psychopathology, discuss prototypes of proposed disorders and comment on future directions within this field.

Internet-related psychopathology

The constant growth of online activities has meant that users stay online longer than before, perhaps resulting in more individuals meeting criteria for addiction [8]. Indeed, early markers of potentially problematic use focused on excessive or longer than intended use of the Internet [9]. By 2010, more than 2 billion people, or about a third of the world population, had access to the Internet, compared with 0.05% in 1990 [10]. Besides increased access, other factors may have contributed to increased Internet use [11]. First, through broadband, smartphones and wireless connections, the Internet has become independent of space and time. Second, the technology has become more affordable as the industry was "scaled" and service providers competed to provide faster connectivity at lower costs. An older but still relevant third factor may be the anonymity of the medium: Internet users may easily disguise their real identity, which results in a greater sense of freedom and control [5]. With rising Internet penetration rates (currently 40% worldwide and 78% in developed countries) [10], the time spent online has doubled over the past decade [12].

Problematic Internet use (PIU) [13], which has also been referred to as "Internet addiction" [14], "computer addiction" [15], "pathological Internet use" [16], "compulsive Internet use" [17], and "impulsive-compulsive Internet Usage Disorder" [18], has been defined in multiple ways (Table I). Most conceptualisations, however, tend to converge on excessive time spent online that is linked to significant downstream impairment and negative consequences [14 19].

Epidemiological estimates of PIU show relatively low prevalence rates (below 1%) [20], with a varying age distribution ("digital natives" at higher risk) [21], sex (slight male preponderance) [22] and geographic area (greater number of cases in developed countries) [23]. High comorbidity rates with other psychiatric disorders (in particular mood, anxiety, impulse control and substance use disorders) are frequent [24]. However, epidemiological studies of PIU are significantly compromised by inconsistency in defining the disorder and lack of inclusion in any diagnostic manual: the APA decided not to include PIU in the latest edition of the DSM [25], despite some pleas in favour of doing so [26]. Instead, an Internet-related problem was mentioned in the appendix to the manual as an area for further research [6].

TABLE I.
Proposed nomenclature of PIU.

Synonyms
Problematic Internet use
Internet addiction
Impulsive-compulsive Internet usage disorder
Internet addiction disorder
Excessive Internet use
Computer addiction
Cyber addiction
Net addiction
Compulsive Internet use
Internet dependence
Internet overuse
Internet-related disorder
Internet behavior dependence
Pathological Internet use

The aetiology of PIU is still largely unknown, but probably involves different psychological, neurobiological and cultural factors. Evidence concerning abnormal levels of dopamine receptors in the striatum of subjects with PIU have been recently reported [27], which is in line with some imaging [28] and neuropsychological [29] data. Taken together, the available data suggest that the pathophysiology is mediated by a prefrontal dysfunction. Such abnormalities may represent a neurobiological vulnerability upon which life events, exposures or individual characteristics act to trigger onset of the disorder, perhaps along a diathesis-stress model [30]. However, it remains to be elucidated whether these neurobiological findings constitute the cause of PIU or are rather the result of neural adaptation and functional plasticity following excessive use.

From a psychopathological standpoint, PIU has been differently conceptualised, including as an impulse-control disorder, such as pathological gambling disorder, a behavioural addiction modelled on substance use disorders, or an obsessive-compulsive condition similar to OCD [31]. Over the past several years, more specific problematic behaviours related to Internet and digital technology use have been described, making PIU a sort of "umbrella" diagnosis including one or more specific psychopathological phenomena.

Specific Internet-related psychopathology

According to the original model by Davis et al. [30], two types of Internet misuse can be identified: "generalised" (which conceptually overlaps with PIU) and "specific". The latter category refers to misuse involving specific content or platforms. While some "specific" entities can be seen as "old" psychopathological phenomena that have been reconfigured by new technologies, others are so intrinsically linked to cyberspace that they can be considered as new problems born out of a new type of interaction between humans and technology [32].

Online Gambling

Gambling disorder is recognised as a mental disorder in the DSM-5, where it is included under non-substance-related use disorders, but the DSM-5 is silent on an independent online variant or online specifier for gambling disorder. However, in its discussion of "Internet gaming disorder" included under "Conditions for Further Study", the DSM-5 states: "Excessive gambling online may qualify for a separate diagnosis of gambling disorder." Some have considered online gambling to be the most addictive form of gambling, linking it to greater impairment [33]. For example, recent data suggest that electronic slots and video-lottery terminals account for nearly 60% of gambling revenue [34]. Still, the common psychopathological explanation of problematic online gambling resembles the classic addiction model with hypothesised abnormality in the brain circuitry involved in decision making (i.e., ventral striatum, ventro-medial prefrontal cortex, midbrain and insula) [35].

Internet gaming disorder

Internet Gaming Disorder (IGD) is a condition in which affected individuals spend excessive time playing video games with ensuing negative consequences on academic, professional or interpersonal functioning. Recent research [36] suggests that IGD may represent a distinct entity from PIU, being characterised by male preponderance, lower levels of depression comorbidity and lower engagement in other internet activities (e.g., social networking). Interestingly, this condition, as opposed to a more general one alluding to all potentially problematic Internet activity, was added to the research appendix of DSM-5, as a potential new diagnosis.

Biological research has demonstrated that IGD subjects may show neuropsychological impairment (e.g., more inhibition errors, possibly due to altered decision-making processes) [37]. Such findings would be consistent with data from recent brain imaging studies which report structural and functional abnormalities of prefrontal, cingulate and insular cortices [38 39]. As with PIU, research into IGD has been considerably hampered by the lack of consensus on its definition and diagnostic thresholds. Thus, reports on prevalence and psychosocial impact vary widely [40].

A unique subtype of IGD may be represented by massively multiplayer online role-playing games (MMORPGs), in which the player interacts with other users via virtual representations ("avatars") in a more immersive environment that often results in more time investment. MMORPGs seem to be associated with specific self-identity and self-efficacy issues [41 42], which may lead to a greater involvement in the online community [43] and to worse personal impact [44].

Cyberchondria

Help-and reassurance-seeking behaviour is hardly a new potentially psychopathological symptom, but the use of the Internet for this purpose has become increasingly more common. Cyberchondria has been defined as excessive or repeated online searching for health-related information that is aimed to calm down health-related anxiety. Paradoxically, such behaviour may increase anxiety in some individuals, usually due to the discovery of new triggers for health-related worries [45]. This "amplification mechanism" may relate to the fact that the Internet was not designed to provide reliable, accurate and unambiguous health information, a fact that may increase uncertainty and worrying [46]. Despite some evidence concerning the association with anxiety and intolerance of uncertainty [47], and despite attempts to formulate it as a multidimensional psychopathological concept [48 49], cyberchondria is still seen as part of the spectrum of classic hypochondriasis [32].

Cybersuicide

The link between PIU, clinical depression and suicide is unclear, with only limited data emerging from methodologically weak studies mostly conducted in adolescents [48]. Nonetheless, some studies report a potential correlation with suicidal ideation or attempts [50-53]. What seems to be relatively more established is a link between specific web content and suicidal behaviour. "Cybersuicide" refers to self-inflicted death promoted by websites that provide the know-how and encourage people to perform suicidal behaviours, sometimes via simultaneous "suicide pacts" [54]. Another form is "webcam suicide", or the online broadcasting of one's suicide using video sharing services, sometimes to an audience that taunts and challenges the victim to commit the act [5].

Psychologically, cybersuicidal behaviours have been explained in terms of strong ambivalence about life, social isolation and the need to share suicidal thoughts [55], although in some cases they may also represent a cry for help. However, the differences between "traditional"

suicide and the online counterpart, as well as the role of culture in this phenomenon, remain to be elucidated [32].

Cybersex

The term "cybersex" describes a wide range of behaviours related to the search for and procurement of sexual pleasure via the Internet. Cybersexual behaviours vary widely and potentially include online dating, viewing of pornographic material, or "cruising" for sex and arranging sexual encounters. However, only those associated with significant personal discomfort or aggressive, coercive or illicit activities can be regarded as pathological [32]. In these situations, the appeal of short-term pleasure leads to failure in controlling the sexual urge, causing long-term negative consequences (e.g., financial or relationship consequences, risk of contracting sexually transmitted infections, legal problems from harassment or sexual exploitation) [56].

Recently, two subtypes of cybersexual behaviours have been described: "receptive", which involves information-seeking and the viewing of sexually explicit Internet content, and "interactive", which refers to the use of websites or social networks for the purpose of engaging in virtual, sexually charged, relationships [57]. The latter behaviour has been also dubbed "cyberaffair" and refers to a romantic and/or sexual relationship that is initiated online and maintained through electronic conversations [57]. Although such behaviours can be harmless, in some cases they may lead to serious consequences due to altered sleep patterns (chat rooms tend to be more active at night), problems with real-life relationships (due to neglect of family and everyday responsibilities, lying to partners and family members), or loss of interest in real-life sex. Older, more educated and less religious individuals have been considered more at risk for cyber-affairs [58].

While Internet sexual addiction has been conceptualised as a variant of PIU [59], a distinct "hypersexual disorder", characterised by increased frequency and intensity of sexual fantasies, urges and enacted behaviours and impulsivity, was proposed but not included in the DSM-5. A proposal for the inclusion of "compulsive sexual behaviour" in ICD-11 has been put forward [60].

Cyberbullying/cyberstalking

Cyberbullying is defined as repeated hostile or aggressive behaviour aimed to inflict harm or discomfort by means of digital tools [61]. Unlike real-life bullying, cyberbullying is not based on the physical superiority of the bully over the victim, since digital technology makes physical strength less important. Digital technology can also make bullying more ubiquitous since it can be carried out anytime and anywhere, with possible amplification of its effects through "viral" dissemination of the victim's humiliation [61]. From a psychopathological viewpoint, cyberbullying has been considered a manifestation of other forms of psychopathology, including antisocial personality disorder and conduct disorder, and has been linked to high rates of psychiatric comorbidity in victims, bullies and bully-victims (victims who become bullies or vice versa) [61].

A related phenomenon, usually described in adults, involves repeated attempts via digital tools (Internet, e-mails, chats, social networks, etc.) to locate and stalk another person. "Cyberstalking" as the behavior has been called may be part of traditional stalking or an independent behaviour [62 63].

Compulsive online shopping

Since the Internet introduced new features of shopping that may potentially make it more "addictive", a new conceptual model for "online shopping addiction" has been proposed, with a psychological and socio-demographic profile that includes: low self-esteem, low self-regulation, negative emotional state, female gender, anonymity and cognitive overload [18]. The psychopathological conceptualisation of compulsive online shopping is mostly based on a classic addiction model, although it maintains some relationship with depression, obsessive-compulsive disorder and hoarding. Materialism and sensitivity to reward play a role in the emergence of this behaviour.

Other Internet-related psychopathology

In some cases, the Internet may play a direct role in promoting pathological behaviours, such as websites that expressly promote unhealthy eating, thus encouraging the emergence of anorexia and bulimia nervosa, with associated negative impact on body image and mood [64]. Similarly, specific online content can contribute to anxiety or affective crises, most tragically when they encourage suicide. A "Twitter psychosis" [65] and the online emergence and magnification of various problematic personality traits [5] have also been described.

Changes in children's lifestyles, including increased time spent playing videogames, have drawn attention to the risks of excessive Internet use in individuals with neurodevelopmental disorders, in particular children with ADHD, who are particularly vulnerable to excessive screen games where visual experiences are privileged over auditory ones and where one operates in brief segments with immediate rewards and without the need for sustained attention [66].

Discussion

One of the first reports on Internet and mental health [67] defined the Internet as a "rapid communication resource"

that was "beginning to have an impact on medicine… and will soon have a major effect on psychiatry". The anticipated effect, however, involved mainly the availability and retrieval of patients' clinical information as well as the communication among scientists and with remote psychiatric settings. Nearly 20 years later, unforeseen psychological cyber-problems have emerged and established "offline" disorders have been transformed by the online experience (Table II).

This is hardly surprising since psychopathology is influenced by social and cultural factors, and since new technologies have already profoundly impacted society and culture. Coupled with the trend to operationally define disorders and to split psychopathology into discrete categories, the opportunity to identify "new disorders" probably tempted many researchers. In addition, media fascination with the Internet and their tendency to blame digital technologies for many negative aspects of modern life may have made it harder for scholars to resist novel nosological categories derived from new behaviours. Al-

TABLE II.
DSM-5 categories with potential "cyber" counterparts.

DSM-5	Internet-related disorders	Proposed examples
Neurodevelopmental Disorders	Favours ADHD	Weiss MD, Baer S, Allan BA, et al. *The screens culture: impact on ADHD*. Atten Defic Hyperact Disord 2011;327-34
Schizophrenia Spectrum and Other Psychotic Disorders	Websites promoting delusional beliefs	Aboujaoude E. *Psychotic Websites*. Psychology Today 2009 (available online at: www.psychologytoday.com/blog/compulsive-acts/200907/psychotic-websites)
Bipolar and Related Disorders	Online manic-like disinhibition	Suler J. *"The Online Disinhibition Effect"*. Cyber Psych Behav 2004;7:321-6
Depressive Disorders	Cybersuicide	Harris KM, McLean JP, Sheffield J. *Examining suicide-risk individuals who go online for suicide-related purposes*. Arch Suicide Res 2009;13:264-76
Anxiety Disorders	Favors anxiety	Chou C. *Incidences and correlates of Internet anxiety among high school teachers in Taiwan*. Comput Hum Behav 2003;19:731-49
Obsessive-Compulsive and Related Disorders	Obsessions about Internet content, compulsive email checking or gaming	Shapira NA, Goldsmith TD, Keck PE Jr, et al. *Psychiatric features of individuals with problematic internet use*. J Affect Disord 2000;57:267-72
Trauma- and Stressor-Related Disorders	Cyberbullying	Tokunaga RS. *Following you home from school: a critical review and synthesis of research on cyberbullying victimization*. Comput Hum Behav 2010;26:277-87
Dissociative Disorders	Dissociative identity disorder associated with internet role playing	TeWildt BT, Kowalewski E, Meibeyer F, et al. *Identity and dissociation in cyberspace. A case of dissociative identity disorder associated with internet role playing*. Nervenarzt 2006;77:81-4
Somatic Symptom Disorders	Cyberchondria	Starcevic V, Berle D. *Cyberchondria: towards a better understandingof excessive health-related Internet use*. Exp Rev Neurotherap 2013;13:205-13
Feeding and Eating Disorders	Websites promoting anorexia and bulimia nervosa	Talbot TS. *The effects of viewing pro-eating disorder websites: a systematic review*. West Indian Med J 2010;59:686-97
Sleep-Wake Disorders	Insomnia due to late night Internet web surfing or gaming	Cheung LM, Wong WS. *The effects of insomnia and internet addiction on depression in Hong Kong Chinese adolescents: an exploratory cross-sectional analysis*. J Sleep Res 2011;20:311-7

(continued)

Table II - Follows

DSM-5	Internet-related disorders	Proposed examples
Sexual Dysfunctions	Cybersex	Southern S. *Treatment of compulsive cybersex behavior.* Psychiatr Clin North Am 2008;31:697-712
Disruptive, Impulse Control and Conduct Disorders	Impulsive/Compulsive Internet Use	Dell'Osso B, Hadley S, Allen A, et al. *Escitalopram in the treatment of impulsive-compulsive internet usage disorder: an open-label trial followed by a double-blind discontinuation phase*. J Clin Psychiatry 2008;69:452-6
Substance Use and Addictive Disorders	Internet Addiction	Block JJ. *Issues for DSM-V: Internet addiction*. Am J Psychiatry 2008;165:306-7
Personality Disorders	Emergence and worsening of personality traits (e.g., narcissism, regression, impulsivity)	Aboujaoude E. *Virtually You: The Dangerous Powers of the E-Personality*. New York: Norton 2012
Paraphilic Disorders	Cybersex	Southern S. *Treatment of compulsive cybersex behavior.* Psychiatr Clin North Am 2008;31:697-712

though whether new technologies have created truly new clinical issues or reshaped old psychopathology remains an open question, it does seem like for many conditions the Internet is more than just a simple "specifier" describing the expression of a disorder. Laying this issue to rest, however, requires more research and a shift from the lack of specificity and incompatible models (i.e., behavioural addiction, impulse control dysfunction, obsessive-compulsive features) that have dominated the field, leading to diagnostic uncertainty and great heterogeneity in reported data. Adding the lack of standardised, properly validated assessment tools, high psychiatric comorbidity and limited treatment options (mostly derived from mother-conditions), it becomes rather easy to support the claim of artificial creation of new psychopathology. Some years ago, Walker [68] warned against this phenomenon by describing a process by which everyday passions could be pathologised. Avid golfers who spend much time golfing, and invest heavily in equipment, may experience discomfort if forced to abstain, and prefer to play golf rather than fulfil occupational or family roles, may similarly be the object of clinical concern, leading to declaring golfing as a new addiction. The same might be said about "addiction" to the Internet, especially if seen as an adaptive response to today's highly wired culture, or if it is a manifestation of introversion, boredom or low mood. Indeed, there is an urgent need to identify proper thresholds for what may constitute PIU, thus creating the basis for reliable epidemiological data.

Given the recent DSM-5 release and the anticipated ICD revision, it is time to reflect on what might constitute an Internet-related mental disorder. Major psychiatric diagnostic manuals still converge on the idea that a mental disorder is characterised by a clinically significant and recognisable pattern of symptoms and behaviours that cause disability, distress and dysfunction. Within such a nosological framework that is defined by graded diagnostic boundaries, clinical thresholds can become blurred or are determined on the basis of medical or moral metaphors [69]. Nonetheless, the choice to include PIU among potential psychiatric pathologies seems rational, even if such an inclusion requires the differentiation of multiple putative clinical entities.

Only future empirical research can determine whether this approach is right. Presently, it must be acknowledged that some specific phenomenological core components of Internet-related psychopathology have been proposed. For example, Kuss et al. [70] discuss six phenomenological core components (salience, mood, tolerance, withdrawal, conflicts, relapse) as the basis for Internet-related psychopathology (see Table III).

In addition, a growing body of neurobiological and imaging studies points to abnormal prefrontal functioning, supporting a biological determinant that may underlie the clinical expression of Internet-related disorders. Finally, reviews of available treatments suggest that potentially effective psychological and pharmacological treatments may be available.

Conclusions

Internet-related psychopathology represents a new challenge to wellbeing that cannot be disregarded. Digital addictions, in particular socially-driven activities, represent the most disabling problems of the DSM-5 "conditions for further studies". More research into the triggers, manifestations and consequences of these activities is needed. Furthermore, cyber-psychopathology is likely

TABLE III.
Core components of Internet-related psychopathology.

Component	Biopsychosocial aspects	Psychopathology
Salience	Cognitive, emotional and behavioural preoccupation with online activities	Obsessive thoughts, craving
Mood	Escape from real-life problems	Mood modifications
Tolerance	Need to stay longer and longer online	Initial addictive behaviour
Withdrawal	Unpleasant feelings when attempting to decrease/discontinue Internet usage	Psychological (e.g., anxiety, depressed mood, irritability) and physical (e.g., somatizations) symptoms
Conflicts	Intra- (subjective feelings of losing control) and inter-personal (family and social relationships) conflicts	Neglect of social/personal responsibilities
Relapse	Unsuccessful attempts to reduce or discontinue Internet use	Chronic course

to represent an even greater challenge to future generations. Actually, more than 30% of children under the age of 2 use a tablet or a smartphone, and 75% of kids aged 8 and younger live in a home with one or more mobile device. What the impact will be of such massive early exposure to digital technology is almost entirely unknown, but there is justifiable concern about the effects on thought processes, attention span and motor and sensory development. Finally, the interventions to confront cyber psychopathologies will have to be expanded beyond still-to-be-tested psychotherapeutic and psychopharmacological treatments to include public health awareness and education campaigns, as well as school-based prevention programs.

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Beyond anorexia and bulimia nervosa: what's "new" in eating disorders?

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Summary

Despite the fact that awareness of eating disorders (EDs) has grown during the past decades, the conceptualisation, psychopathological characterisation and clinical diagnosis of EDs has proven to be problematic for both researchers and clinicians. Presently, diagnostic criteria employed for anorexia nervosa (AN) and bulimia nervosa (BN) are unable to account for an exceedingly high number of individuals with clinically significant eating symptoms or to properly address new clinical prototypes of ED. The aim of this paper is to describe the developments and current limitations of EDs diagnoses, and to recapitulate the recent literature on emerging phenotypes. Descriptions of the symptoms and behaviours of ED patients with diabulimia, orthorexia, muscle dysmorphia, drunkorexia and nocturnal eating disorders are featured with special focus on psychopathological classification and diagnostic ambiguity issues. An overview of non-specific eating and feeding disorders (EDNOS) in the newly released DSM-5 eating and feeding disorders section is also provided. Given the frequent transition between different phenotypes in patients with EDs and the common occurrence of individuals with clinically significant eating symptoms who evade diagnostic criteria, a better understanding and categorization of emerging EDs is required to guide psychiatric research and improve clinical outcomes.

Key-words

Compulsive behavior • Diabulimia • Drunkorexia • Eating disorders • Feeding disorders • Night eating syndrome • Orthorexia • Psychopathology • Vigorexia

Introduction

The first descriptions of self-starving for religious purposes dates to the Hellenistic era of the Roman Empire, and many anecdotal reports concerning disordered eating behaviours have continuously appeared throughout subsequent centuries [1]. However, the first medical description of anorexia nervosa (AN) is usually attributed to the British physician Richard Morton in 1689. A more in-depth psychiatric approach to abnormal eating behaviours is attributable to the French neurologist Ernest C. Laségue and to the English physician Sir William W. Gull, who introduced the term "anorexia nervosa" [2]. In 1873, both authors, almost simultaneously but yet independently, published seminal papers concerning the causes, clinical picture and course of AN [3]. Up to the second half of the 20th century, eating psychopathology paled in the shadows of psychiatric care and it received little scientific interest. Only after the publication by the German-American psychoanalyst Hilde Bruch of the book "The Golden Cage" [4], disordered eating behaviours came to the attention of the general, medical and psychiatric audiences. This event was coupled with the other major prototypical eating disorder (ED) (i.e., bulimia nervosa; BN) being first described in 1979 [5]. Although awareness of EDs has constantly grown during past decades, their conceptualisation, psychopathological characterisation and clinical diagnosis has remained somewhat problematic. According to Uher and Rutter [6], the nosological formulations of ED in both ICD-10 and DSM-IV were unsatisfactory for different reasons, including failure to characterise patients at various developmental stages, lack of continuity between childhood and adult feeding disorders and the difficulties in routine practice using those diagnostic criteria in both clinical practice and research settings. One of the main concerns of such clinical criteria is lack of/poor sensitivity and specificity: many patients presenting clinically significant eating-related psychopathology do not fulfill the diagnostic criteria, which in the end account only for a minority of affected individuals.

To settle such problems, both the American Psychiatric Association and the World Health Organization made significant changes in the latest revisions of DSM and ICD, respectively. ICD-11, for example, promises greater attention to cross-cultural validity, a more cogent life-course characterization, a more pronounced prototypical approach with greater modulation of diagnostic thresholds (e.g., a uniform 4-week criterion for the illness duration) and a revision of diagnostic boundaries to avoid the

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inflation of "other disorders" categories. Unfortunately, as the ICD revision process has just entered its "beta phase" (2013-2017) and the revision process will be completed by the year 2018, many years will have to elapse before the impact of ICD-11 on ED clinical diagnosis and psychopathological conceptualisation can be determined.
The newly produced DSM-5 [7] attempted to correct the flaws of its previous edition, with the explicit aim to better represent the symptoms and behaviours of ED patients across their life-span. The most substantial changes introduced in the DSM-5 section on "Eating and Feeding Disorders" are the revision of the diagnostic criteria for AN (more focused on observable behaviours and with the amenorrhoea no longer needed for the diagnosis), and for BN (reduced frequency of binge eating and compensatory behaviours). In DSM-5, greater attention is given to binge eating disorder (BED) as a stand-alone diagnostic category, whereas three previously listed disorders within the "disorders usually first diagnosed in infancy, childhood or adolescence" are also included. The above changes were expected to minimise the use of catch-all diagnoses (e.g. "other specified", EDNOS, or "unspecified" eating disorders) and make EDs diagnoses easier for the clinician. Several recently published studies are in line with such expectations: for instance, the use of DSM-5 criteria was associated with significantly less frequent residual eating disorder diagnoses in 150 adolescent and young adult residential female patients [8], in 117 community outpatients [9], 309 outpatients [10] and even among adolescents from the community [11].
Nevertheless, current diagnostic criteria for AN and BN still do not account for the majority of individuals with clinically significant eating symptoms and new clinical prototypes for EDs have been described. The aim of the present paper is to provide an overview of the recent literature covering some of the emerging alleged EDs.

Diabulimia

Type 1 diabetes mellitus is an inflammatory autoimmune disease that leads to the destruction of insulin-producing pancreatic cells resulting in a lack of insulin. Besides having to take into account food intake and energy expenditure, in order to avoid hypo- and hyperglycaemia, multiple daily doses of insulin must be administered to diabetic patients. As the majority of patients with type I diabetes are children or adolescents, they may represent a high-risk population for ED. Recent reports highlight that adolescents with type I diabetes are twice as likely to experience an ED as non-diabetic ones [12] by exhibiting difficulties in maintaining optimal weight with increased risk of concerns about weight and body shape. Having abnormal eating behaviour in patients with diabetes can be especially challenging in order to keep glycaemia under control since insulin encourages fat storage. Consequently, many people with type I diabetes attempt to reduce their insulin injections in order to induce/provoke weight loss [13 14].
The word 'diabulimia' refers to the deliberate omission or reduction of insulin use in individuals with type 1 diabetes with the specific purpose of weight control [15]. The association of intentional hypoglycaemia in patients with type I diabetes and BN/EDNOS has been recently reported [16 17].
Diabulimia does not represent a fully recognised medical condition yet, but it is receiving growing attention. The American Diabetes Association has acknowledged the existence of this condition for quite some time [18] and it has been estimated that between 30 and 40% of adolescents and young women with diabetes skip insulin after meals [19]. The lack of proper insulin treatment may lead to many harmful conditions spanning from the short term risk of dehydration, breakdown of muscle tissue and fatigue, and kidney failure, retinopathy and cardiovascular and neuropathic complications over the long term [20]; thus, diabulimia represents a potentially life-threatening disorder requiring immediate medical attention [21]. Furthermore, recent reports on the coexistence of type I diabetes and AN highlight the possible increased incidence of known diabetic complications (such as retinopathy and nephropathy) and peculiar difficulties in glucose control especially during "refeeding" phases [22]. These patients also present lower motivation to change their eating behaviours and a generally poorer prognosis [17].
Specific screening questionnaires [23] and biological methods have recently been proposed to diagnose diabulimia. *Glycosylated haemoglobin* (HbA1c) is usually higher in diabetic patients with and without EDs, and the HbA1c pattern allows for the detection of intentional insulin omission for weight loss (usually with a pattern of initially stable HbA1c levels followed by both high HbA1c levels and wide fluctuations between visits) [14 24].
At present, neither specific diagnostic nor treatment guidelines are available [25]; when diabetes and EDs co-occur, the clinician is left to make generic recommendations on the adherence to insulin treatment and correct diabetes self-management, in order to prevent complications in susceptible patients with only a generic focus on psychopathology and eating patterns.

Orthorexia

Orthorexia is a term used to describe a pathological obsession for "healthy" or "pure" food (e.g., free of herbicides or pesticides), with rigid avoidance of food believed to be unhealthy or polluted [26]. The term "orthorexia" is derived from the combination of the Greek words "orthos" (which means accurate, right, correct, valid) and

"orexsis" (which means hunger or appetite); the term is often used to designate an "obsession for healthy and proper nutrition" [27]. Of course, healthy eating habits are not pathologic *per se*; however, excessive preoccupation about consuming healthy food, spending an excessive amount of time on food thoughts, and experiencing associated dysfunctions suggest disturbed behaviour and/or personality [28], and the disorder has been often dubbed as "a disease disguised as a virtue".

Although many hospital admissions might potentially be due to orthorexia, at least in the USA [29], the disorder is not yet classified in any psychiatric diagnostic manual due to insufficient evidence. According to Donini et al. [28], the prevalence of orthorexia in the general population is about 7%; however, in high-risk groups (such as healthcare professionals, dietitians or artistic performers) the prevalence may rise to approximately 50% [30]. Segura-Garcia et al. [31] reported that orthorexia symptoms are highly prevalent among patients with a previous diagnosis of AN or BN, with a tendency to undergo clinical improvement in AN and BN and migrate towards less severe forms of EDs [32].

Typically, orthorexic individuals 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 are either vegetarians, vegans, frugivores (i.e., eat only fruit) or crudivores (i.e., eat only raw food); furthermore, orthorexics typically refuse to eat away from home (due to lack of trust towards food preparation) and tend to feel morally superior, self-righteous and are at increased risk of social isolation [33].

Such a restrictive dieting attitude may lead to several nutritional deficits and medical complications (such as osteopenia, anaemia, pancytopenia, hyponatraemia, metabolic acidosis and bradycardia), which closely resemble the quali-/quantitative malnutrition status typical of AN [34].

Several diagnostic criteria [35] and rating scales (e.g., the ORTO-15 by Donini et al. [36]) for orthorexia have been proposed, but they have been only partially validated. Items are focused mainly on the "obsessional" preoccupation with eating "healthy foods", associated with significant psychosocial impairment after exclusion of other psychiatric, non-psychiatric and religious issues.

From a psychopathological viewpoint, orthorexia has been closely linked to AN and obsessive-compulsive personality/disorder [37]. The presence of recurrent, intrusive thoughts about food and health heighten worry over contamination and impurity. The overwhelming need to investigate source, processing and packaging of foods and to arrange food and eat in a ritualised manner make these behaviours similar to obsessive compulsive modalities, although with a highly ego-syntonic perception. Moreover, subjects with orthorexia seem to share

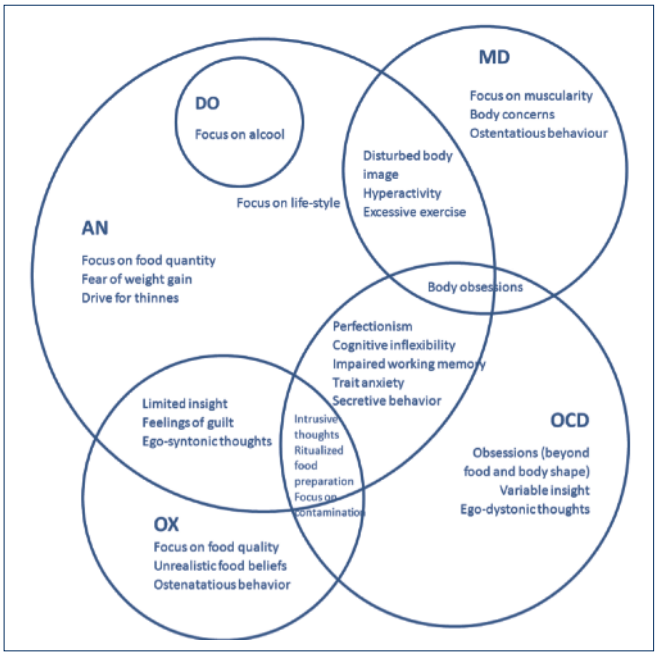

FIGURE 1.
Venn diagram representing the possible relationships between established and putative eating-related disorders (AN: anorexia nervosa; DO: drunkorexia; MD: muscle dysmorphia; OCD: obsessive-compulsive disorders; OX: orthorexia).

common traits of perfectionism, anxiety, need to exert control and valuing diet adherence as a proof of self-control (and deviation from the diet as a failure of self-control) with AN. Therefore, there is still an open debate regarding whether orthorexia is a unique disorder or just a subtype of anorexia or obsessive-compulsive disorder [38]. The empiric investigation of motivations and body perception (e.g., pursuit of an ideal body shape vs. keeping an healthy body), of ideation toward eating and food (e.g., worries about quantity vs. quality of food), of the level of illness insight/awareness (subjects with AN try to hide their habits whereas orthorexic individuals allegedly show off their behaviour) and of socio-demographic characteristics (e.g., sex distribution, level of education, access to food-related information) in clinical populations will probably shed further light on the true psychopathology of this syndrome. At present, orthorexia would most appropriately be categorised, within DSM-5 options, as "avoidant/restrictive food intake disorder" (ARFID), although it has been suggested that it may represent a distinct subtype [39].

Muscle dysmorphia

Muscle dysmorphia (MD), also known as "vigorexia" or "bigorexia", is a body image-related psychological con-

dition in which normal or even unusually muscular; affected persons demonstrate an excessive focus on body appearance associated with the fear of being "small" or "puny". Such fear leads to unwarranted physical exercise and increased body size [40]. Usually, pathological preoccupation with one's degree of muscularity causes severe subjective distress, impaired social and occupational functioning (due to the feelings of shame over their perceived appearance flaws and to their excessively time-consuming exercise schedule), and frequent abuse of anabolic steroids or other similar substances in an attempt to gain size [41]. Due to lifestyle modifications and substance abuse, MD can lead to serious health complications such as damage to muscles, joints and tendons, fatigue, acne, testicular atrophy, decreased sperm count, high blood pressure, high cholesterol, abnormal liver function, constipation, retention of water and intestinal gas [42].

Although male body builders are thought to be at higher risk for MD, the few available studies tend to report that the number of affected females is increasing in relation to higher body image dissatisfaction and greater concern over physical appearance [43]; however, no definitive figures regarding the real incidence of MD in the general population are yet available.

The condition was first observed by Pope et al. [44] in a sample of male body builders and was originally conceptualised as a "reverse" or "opposite" form of AN mainly because of the antithetical symptomatology in relation to body size. Indeed, individuals with MD tend to see their body size as excessively "small" and/or "weak" and, even though they may look normal or highly muscular, they wish to be larger and more muscular. Specific diagnostic criteria have been proposed for DM (Table I).

Despite continued investigation on the topic, contention surrounds MD nosology as it has been classified in different categories, with little consensus among researchers and clinicians. Over the years, MD has been linked to at least four different psychopathological realms: EDs, obsessive-compulsive disorder, body dysmorphic disorder and, more recently, behavioural addictions (in this case, addiction for a perfect muscular body [45]). To reveal the psychopathological conundrum behind the diagnosis of MD [46], one could reflect on the fact that, although being historically conceptualised as a "reverse" eating disorder, MD should be classified as an obsessive-compulsive disorder within the DSM-5 and as hypochondriacal disorder within the ICD-10. Recent trends in psychopathology seem to favour the idea that it should be treated as a body dysmorphic disorder, in which a "muscle dysmorphia" specifier may have clinical utility [47 48]. In order to define if MD really belongs to the EDs spectrum, a thorough exploration of the psychopathological elements associated to the syndrome (i.e., body mass, media influences, ideal body internalisation, low self-esteem, body dissatisfaction, health locus of control, negative affect, perfectionism and body distortion [49]) is needed. A better understanding of the core psychopathology could guide psychiatric research and clinical practice as treatment for MD has to date largely utilised selective serotonin reuptake inhibitors and CBT only on the basis of uncontrolled case series and reports [50].

TABLE I.
Proposed diagnostic criteria for muscle dysmorphia [42].

A. Preoccupation with the idea that one's body is not sufficiently lean and muscular. Characteristic associated behaviors include long hours of lifting weights and excessive attention to diet
B. The preoccupation is manifested by at least two of the following four criteria: 1. the individual frequently gives up important social, occupational, or recreational activities because of a compulsive need to maintain his or her workout routine and diet schedule 2. the individual avoids situations where his or her body is exposed to others, or endures such situations only with marked distress or intense anxiety 3. the preoccupation about the inadequacy of body size or musculature causes clinically significant distress or impairment in social, occupational, or other important areas of functioning 4. the individual continues to work out, diet, or use ergogenic substances despite knowledge of adverse physical or psychological consequences
C. The primary focus of the preoccupation and behaviors is on being too small or inadequately muscular, as distinguished from fear of being fat as in anorexia nervosa, or a primary preoccupation only with other aspects of appearance as in other forms of body dysmorphic disorder

Drunkorexia

Drunkorexia is used to describe a disorder characterised by restricting food assumption, before alcohol is consumed or planned to be consumed, in order to avoid calorie intake [51]. Literature on the topic is very scarce, with only 6 related articles available in PubMed at the present moment. The available evidence tend to support the idea that drunkorexia is a relatively common activity among US college students with a reported 46% of prevalence within this population [52]. Young age, female sex, physical exercise, abnormal eating and heavy-drinking behaviours have been associated with a higher risk of develop-

ing drunkorexia [53 54]. As this disorder combines the worse of drinking and the worse of dieting, the consequences involve not only drinking excessively on an empty stomach, but also dangerously altering nutrition.
Although a questionnaire providing a multidimensional measure of specific motivations and behaviors of drunkorexia has recently been proposed [55], it has not been validated yet.
Even though some authors [56] recently proposed that drunkorexia might be specifically related to weight concerns in line with the higher incidence among female heavy-drinkers with respect to males, the psychopathological characterisation of the syndrome is still very rudimental. Further studies are needed to design focused interventions, which might aid in to safely reconciling pressure to be thin and participate in binge drinking.

Nocturnal eating disorders

Nighttime eating might occur in a variety of psychiatric syndromes, ranging from atypical forms of depression to binge eating. Moreover, two major psychiatric clinical entities characterised by abnormal meal timing have been described: "nocturnal eating syndrome" (NES) and sleep-related eating disorder (SRED).
NES was defined almost half a century ago by Stunkard et al. [57] as abnormal meal timing with nocturnal hyperphagia and morning anorexia, insomnia and awakening, in the absence of daytime EDs it typically occurred during periods of stress and was associated with poor outcomes of efforts to reduce weight. Throughout the years, NES has been conceptualised [58 59] as a proper sleep disorder (and classified within the *First International Classification of Sleep Disorders*) or as a circadian rhythm disorder (with food intake being shifted towards the end of the day, interfering with sleep and decreasing satiety). Besides sleep reduction and fragmentation, the high scores obtained on several psychometric scales for eating symptomatology suggest that NES is psychopathologically related to EDs, although the amount of food consumed in the evening/night is not necessarily large and its disordered eating pattern is not better explained by BED, nor is any loss of control over food intake required [60 61]. Due to its high comorbidity with obesity and other psychiatric conditions, NES represents a specific focus of attention for clinical care. Recent reports tend to confirm that NES is prevalent among psychiatric outpatients and associated with depression, impulse control disorder and nicotine dependency, especially when high degrees of body dissatisfaction are present [62 63].
Nonetheless, and in spite of the availability of several specific psychometric tools, NES is often neglected by both health professionals and patients [64] and is practically ignored by major diagnostic systems (DSM-5 relegated it to the EDNOS category). However, the latest revision of its diagnostic criteria [65] (Table II) might increase the validity of the NES diagnosis and favour its inclusion in future updates of psychiatric diagnostic systems.
Another condition that poses a link between disordered eating and sleep dysfunction is SRED, which is characterised by recurrent episodes of eating at the transition from night-time sleep to arousal, with preference for high-caloric foods [66]. The level of consciousness during SRED may vary widely (from partial consciousness to complete unawareness) and this might create some diagnostic ambiguity between SRED parasomnias and somnambulistic episodes [67]. Furthermore, SRED is frequently associated with the use of psychotropic medications (particularly sedative-hypnotics) and other sleep disorders [68]. Although it seems to share some pathophysiologic features with NES, several other aspects tend to clearly differentiate SRED from the latter and make it a candidate psychiatric disorder [69].

TABLE II.
Proposed research criteria for NES [65].

A. The daily pattern of eating demonstrates a significantly increased intake in the evening and/or nighttime, as manifested by one or both of the following: 1. at least 25% of food intake is consumed after the evening meal 2. at least two episodes of nocturnal eating per week
B. Awareness and recall of evening and nocturnal eating episodes are present
C. The clinical picture is characterized by at least three of the following features: 1. lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week 2. presence of a strong urge to eat between dinner and sleep onset and/or during the night 3. sleep onset and/or sleep maintenance insomnia are present four or more nights per week 4. presence of a belief that one must eat in order to initiate or return to sleep 5. mood is frequently depressed and/or mood worsens in the evening
D. The disorder is associated with significant distress and/or impairment in functioning
E. The disordered pattern of eating has been maintained for at least 3 months
F. The disorder is not secondary to substance abuse or dependence, medical disorder, medication, or another psychiatric disorder

Other eating disorders

Some other clinical syndromes related to abnormal eating behaviour have been reported during the past decades. For the majority of them, many nosological controversies, mainly due to their relative clinical rarity and the consequent scarcity of empirically grounded data, still persist; given the concerns about their real prevalence in the general population and their long-term course, only some of these have been included in DSM-5 and will be probably included in the upcoming ICD-11. A brief account of the disorders most frequently reported in the literature is provided in Table III.

Conclusions

The psychopathological definition of "non-threshold" EDs is still blurred, at least for some syndromic entities. However, given the fast rate by which alleged "new" EDs are described in the scientific literature, the field still requires

TABLE III.
Non-specific eating and feeding disorders and their inclusion into the DSM-5 eating and feeding disorders section.

Proposed eating syndrome	DSM-5 inclusion	Clinical features
Adult Pica	Yes	Pica is the persistent eating of non-food substances (including earth, chalk, metals, plastic objects, hair, faces, etc.). Traditionally included in the major diagnostic systems among conditions usually occurring during infancy or childhood, DSM-5 has recognized that adult presentations of pica may persist. Presently pica typically is given attention during adulthood, but the diagnosis is made only if the condition is severe, leads to adverse consequences and happens outside cultural or religious practices (Nicholls & Bryant-Waugh, 2009). Pica is frequently diagnosed during pregnancy and among people with intellectual disabilities and is rare among the general population, but recent reports tend to show that the prevalence of related behaviors might be higher among people with ED (Delaney et al., 2015)
ARFID	Yes	DSM-5 renamed infancy or early childhood feeding disorder as "avoidant/restrictive food intake disorder"(ARFID), adding significantly expanded criteria (Norris &Katzman, 2015). The syndrome, also dubbed "selective eating disorder", is characterized by the inability to eat certain foods and strong preference for "safe" foods. Individuals may exclude whole food groups (such as fruits or vegetables) or the refusal maybe be based just on color or on specific brands. Patients with ARFID seem to be clinically distinct from those with AN or BN, as they tend to be significantly underweight with a longer duration of illness and a greater likelihood of comorbid medical and/or psychiatric symptoms (Fisher et al., 2014)
Choking phobia	No	Also known as "anginophobia", "phagophobia" or "swallowing phobia", this is rare clinical entity that is characterized by the phobic stimulus of swallowing that results in the avoidance of food or drinks, and ultimately to low weight, social withdrawal, anxiety and depression states (Lopez et al., 2014)
Emetophobia	No	Emetophobia is an intense and irrational anxiety pertaining to vomiting and/or nausea, which may lead to food avoidance and weight loss, because of its intense somatization mechanism (Boschen, 2006). The disorder is often hidden because of the associated shame among sufferers. Very little empirical data are available concerning its epidemiology, treatment and outcome. It is classified among specific phobias in ICD-10 and DSM-5 and seems to be comorbid with anxiety and depressive disorders, rather than with eating disorders (Sykes et al., 2015)
Food addiction	No	It has been proposed that some kind of foods may be potentially addictive and thus cause overeating and, in turn, obesity (Meule & Gearhardt, 2014). However, several concerns have been expressed with regard to the shift of focus from "eating addictive" behavior to the substance-based addiction model, especially because of the lack of systematic clinical and translational studies in this field (Hebebrand et al., 2014)
Grazing	No	Grazing is a relatively frequent behavior characterized by a repetitive eating pattern, often following bariatric surgery; since it has also been reported in eating disordered and community samples, and given its negative impact on weight outcomes after bariatric surgery, it is receiving greater attention, though the use of different definitions has prevented accurate measurements and comparison of data across studies (Conceição et al., 2014)

(continued)

Table III - Follows.

Proposed eating syndrome	DSM-5 inclusion	Clinical features
OSFED	Yes	The "Other Specified Feeding and Eating Disorders" (OSFED) have been included in the DSM-5 to specifically include all ED which do not fall into the ED "threshold"; recent investigations tend to highlight that it is difficult to discriminate OSFED from threshold ED because of genetic risk, prevalence and impairment (Fairweather-Schmidt & Wade, 2014)
Post-bariatric eating disorders	No	Specific forms of AN following bariatric surgery have been recently reported to persist even after long-term follow up and seem to be characterized by high degrees of disinhibition and impulsiveness (Tortorella et al., 2015). Current empirical evidence for the alleged disorder is very limited to distinguish it from other forms of AN. However, a recent literature review (Opolski et al., 2015) has proposed that many different eating -related psychopathological entities might follow bariatric surgery (i.e., binge eating disorder, grazing, night eating syndrome, emotional eating, food cravings and addiction, and pre-surgical expectations of post-surgical eating). Further investigations are required to define the prevalence, impact and characteristics of such conditions
Purging disorder	Yes	Purging disorder was recently included as an otherwise specified feeding or eating disorder (OSFED) in the DSM-5 and is characterized by characterized by recurrent purging behaviors (such as self-induced vomit, misuse of laxatives, diuretics or enemas) to control weight or shape, in the absence of binge eating episodes, in people with near-normal or normal weight; however, limited evidence is available on its prevalence, psychopathological characteristics and etiology (Munn-Chernoff et al., 2015)
Regurgitation disorder	Yes	Regurgitation disorder refers to the repetitive bringing back to mouth, spitting or re-chewing of previously swallowed food from the stomach. It was included in ICD-10 and DSM-IV under the name of "rumination disorder". However, since rumination is often used also to describe repetitive thinking in psychopathology, renamingthe syndrome as "regurgitation disorder" has recently been proposed (Uher & Rutter, 2012)
UFED	Yes	DSM-5 lists an "unspecified feeding and eating disorder" (UFED) category, for those subjects whose symptoms do not meet any other diagnostic category but still cause clinically significant distress or impairment. Recent research suggested that within this category most of the cases are atypical forms of anorexia and overweight subjects struggling to lose weight and focusing on body weight/shape concerns (Wade & O'Shea, 2015)

great clinical attention by researchers and clinicians. Despite numerous biological, psychological and physical hallmarks of EDs have already been identified, and the role of environment has been recognised to increase the risk for disordered eating, the comprehension of potential new disease patterns is still superficial. Grasping emerging ED phenotypes in-depth is especially challenging because of symptom overlap and rapid transition between different phenotypes over time. Understanding whether they are new clinical entities or whether they encompass an existing major eating disorder will aid clinicians in managing such patients and policy makers in implementing prevention programs for vulnerable groups.

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Migration history, minorities status and risk of psychosis: an epidemiological explanation and a psychopathological insight

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Summary

Objectives

A marked increased incidence of psychosis in migrants and ethnic minorities is a well established phenomenon. We aim to review data and insights arising from epidemiological and clinical/psychopathological studies regarding the relationship between migration history, minority status and risk of psychosis in order to evaluate the experiences of migrants and minority ethnic groups in host societies.

Method

A qualitative literature review was conducted to identify population surveys, services based studies, and clinical and biological studies on the relationship between migration and/or minority status and psychosis. Studies were identified by searching MEDLINE, PsychINFO and EMBASE. The search was supplemented by references provided by personal bibliographies of the investigators and by hand searching content pages of journals considered relevant to the topic. The search was run in June 2015.

Results

Risk differences related to minority groups vary in different countries. Socio-environmental risk factors faced by origin groups operate differently in the countries, depending on social experiences and available resources to cope with adversities. In addition, social factors can represent environmental risk factors because they might regulate gene expression. Facing severe or chronic social stress, such as isolation, low socio-economic status, late-life social adversities may result in long-term sometimes permanent alterations of the biological stress-response system, which can lead to the development of physical and mental illnesses. A number of studies have taken into account psychopathological and clinical features at psychosis onset and follow-up, and they do not support the suggestion that misdiagnosis can explain the high rates found in those populations.

Conclusions

Reviewed papers cover a period of more than 30 years and highlight that history of migration and minority status might both be important in increasing the risk of psychosis. Clinical studies reported that psychopathological differences and misdiagnosis cannot explain the excess of psychosis found in migrants and ethnic minorities. The excess of psychosis in migrant and ethnic minorities may be at least attenuated by several psychosocial interventions, targeted at social disadvantages and at most at-risk individuals and populations.

Key words

Migration • Ethnic minorities • Psychosis • Cultural competent psychopathology

Background: psychosis, migration and minorities

The first studies showing an increased incidence of schizophrenia and other psychotic disorders in migrants date back to the 1930s, when Odegaard [1] noted a markedly increased incidence of hospital admission rates for schizophrenia in Norwegian immigrants in the United States compared with Norwegians who did not migrate. The author hypothesised that the explanation for the excess of psychosis amongst his fellow immigrants was that the more vulnerable migrated; this theory was called "selective m igration". However, several pieces of evidence have disconfirmed this hypothesis, and called the attention of epidemiologists to environmental factors that can explain the so-called "excess of psychosis" in immigrants. As second generation migrants have grown up, there has been a further unexpected rise in the incidence of psychotic disorders in the second generation [2 3],

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thereby making it likely that social factors may be playing a part in the genesis of psychosis among migrants. Moreover, even Odegaard [1] observed that rates were higher among immigrants who had been in the US for 10-12 years, suggesting that environmental factors in the hosting countries could play an important role. Studies conducted in Jamaica [4], Trinidad [5] and Barbados [6] have revealed incidence rates of psychosis lower than those observed in migrants from these countries to UK. In addition, there is no evidence that biological risk factors for schizophrenia (such as obstetric complications and viral infections) are more common or have a greater effect in the Black-Caribbean immigrant population [7].

Risk differences related to minority groups varies in different countries [3]: in the UK, Black minorities show the highest risk, while in the Netherlands the highest risk is among more recent North African migrants. In Italy, Eastern Europeans are reported to have the highest risk of developing psychosis [3]. Thus, it is intriguing to try to understand what characteristics of each specific host society interact with each specific type of migration and/or minority groups (first- or next-generation; economic or political migrants, etc.) to increase the risk of psychoses. It seems necessary to look for the risk of psychosis in the experiences and circumstances of migrants and minority ethnic groups in majority societies. We aim to review data and insights arising from epidemiological and clinical/psychopathological studies on the link between migration history, minority status and risk of psychosis.

Method

A qualitative literature review was conducted to identify population surveys, services-based studies, and clinical and biological studies on the relationship between migration and/or minority status and psychosis. Studies were identified by searching MEDLINE, PsychINFO and EMBASE. The search was supplemented by references provided by personal bibliographies of the authors and by hand searching content pages of journals considered relevant to the topic. The search was run in June 2015.

Results

The excess of psychosis in minorities: the epidemiological explanation

Recently, the excess of psychosis among migrants and minorities has been considered a phenomenon linked to the complex interactions between biological vulnerabilities and environmental factors (cultural and socio-economic) during the entire migration process and settlement [8]. The proposed environmental factors, which can act both individually and socially, can schematically be placed in the three phases of the migration process [9]: the pre-migration phase (obstetric complications, infectious factors, nutritional deficiency), the migratory phase (trauma of the journey, preparing to migrate, etc.) and during post migration phase (discrimination, unemployment, low socio-economic status, racism, isolation, "urbanicity" and ethnic density). Of course, for second and subsequent generation migrants, all factors occur in the "post-migration" phase, i.e. during the period of living as a minority in a majority society. As already noted [9], most of the available studies have been carried out in the post-migratory phase, and thus refer to settled minorities more than migrants. The AESOP study [10] has pointed out the following factors can be considered as possible candidates for the excess of psychosis in migrants: death or separation from parents before the age of 16 years; social isolation, social disadvantage and the perception of social disadvantage; the "mismatch" between expectations and achievements; strong cultural identity (which exacerbates the distance between minorities and majorities, found more frequently in minority cases rather than in controls).

To our knowledge, the study by Boydell et al. [11] is the first one to explore contextual variables. This historical cohort study (1988-97) carried out in South East London highlighted a "dose response" variation of incidence of psychosis with respect to the ethnic minority density in the area. The relative risk of psychosis for minorities who live in areas with low ethnic density (less than 22%) was about twice (RR 4.4) the risk of those living in areas of high density (RR 2.4). According to the authors, this finding may indirectly confirm the epidemiological importance of social networks in protecting individuals from stress factors that can contribute to psychosis onset.

Later, several studies have evaluated the effect of neighbourhood variables, showing that the incidence of schizophrenia is heterogeneous and lower in areas where white British and minority groups live in more cohesive and less fragmented milieu [12]. Consequently, the variance in the incidence of psychosis in South East London cannot be explained only on the basis of individual variables such as age, gender and ethnicity. Socio-environmental risk factors, measured at the level of neighbourhood (such as voter turnout, ethnic density, ethnic fragmentation, socio-economic deprivation) may help to explain this heterogeneity [12]. One hypothesis is that social capital may mediate the effect of these variables, in agreement with the hypothesis made by Faris and Dunham [13], who speculated that the highest rates of schizophrenia were in more disorganised cities, not necessarily in the poorest.

History of migration, stress and psychosis

Some studies added weight to the evidence about the relationship between cumulative stress during life following migration and excess of psychosis in migrants. In Malmo, researchers found that in first generation immigrants who developed psychosis, over 50% had resided in Sweden for 10 years or longer, prior to their first contact for psychotic symptoms, suggesting that the risk associated with migration might accumulate over time [14]. Moreover, the highest risk for psychotic disorders among immigrants in the Netherlands was predicted by younger age at the time of migration [15]. These studies contradict the selective migration hypothesis and propose instead that younger age at migration and duration of migration are predictive of the risk for psychosis, suggesting that duration of exposure to the host country is relevant.

Cantor-Graae and Pedersen [16] examined the full range of psychiatric disorders associated with any type of foreign migration background among persons residing in Denmark, including foreign-born adoptees, first- and second-generation immigrants, native Danes with a history of foreign residence and persons born abroad to Danish expatriates. They found that all categories of foreign migration background, except persons born abroad to Danish expatriates, were associated with increased risk for at least one psychiatric disorder. They confirmed the two-fold risk for developing schizophrenia and schizophrenia spectrum disorders for first- and second generation immigrants in Denmark. In particular, first- and second-generation immigrants having two foreign-born parents showed significantly elevated incidence rate ratios (IRRs) for schizophrenia and schizophrenia spectrum disorders. The authors hypothesised that persons having two foreign-born parents may have greater visibility than those with only one foreign-born parent because of greater differences in physical or behavioural characteristics, and that they might be particularly vulnerable to feel different or excluded from the rest of society. Therefore, some migrants may be especially challenged by their greater visibility or "otherness" in the Danish society. Another important result of this study is that the migrant group most at risk of developing mental illness was constituted by foreign-born adoptees. This group of people could represent "the extreme" of the migration dimension within the psychosis risk-perspective and to be foreign-born adopted could mean a greater exposure to all the social and environmental factors that make migrants particularly vulnerable to psychosis, such as separation from parents and early age of migration.

The Italian context

The Italian scenario is interesting because migration is a recent phenomenon, with the consequence that almost all migrants are first generation migrants. A higher incidence rate of psychosis among migrants compared to natives has been reported in Bologna [17]. In a large epidemiologically based cohort study of first-episode individuals (Psychosis Incident Cohort Outcome Study, PICOS) collected in the Northern-Eastern part of Italy, it was found that immigrants (the majority of whom came from Eastern Europe) had markedly high incidence rates for all psychoses than the Italian population (IRR 2.26, 95% CI 1.85-2.75) [18]. In Bologna, migrants with FEP were more often married and living outside the family of origin, while they showed a lower substance and alcohol use rate compared to natives with FEP [19]. Data from Italian studies suggest that not only belonging to a minority group is a condition associated with higher risk of psychosis, but also being a recent migrant.

Psychopathological insight and cultural competent view of the phenomenon

A strong critique to the studies of psychosis in minorities comes from cross-cultural perspectives. Several studies show possible misdiagnoses of mental disorders in migrant patients [20 21], which might be due to a peculiar clinical presentation and/or to the different expressions of suffering across cultures [22]. Some authors have suggested that there are possible misunderstandings between doctors and patients with religious beliefs and traditions different from Western ones and, as a consequence, emotional distress in these populations may be misdiagnosed as schizophrenia or psychosis [23]. Consistently, Cantor-Graae et al. [14] found that 25% of first episode psychosis patients have different diagnoses at 3 to 5 years; the majority of patients with a diagnosis of conversion at follow-up were immigrants. On the other side, previous research has shown unusual psychopathological expressivity of psychotic disorders in first-generation migrants; such disorders might present themselves either with core somatic symptoms or with more prominent mixed affective symptoms than native patients [24]. Moreover, in a sample of psychotic patients, King et al. [25] identified a higher prevalence of unusual psychotic syndromes in first-generation migrants than in native patients. This evidence might be due to the action of what Kirmayer and Young call "cultural idioms of distress" that are "culturally prescribed modes of understanding and narrating health problems and broader personal and social concerns" [26]. In this view, "symptoms can be understood as moves within a local system of power": in migrants, "certain symptoms have been interpreted as being forms of 'resistance' or 'weapons of the weak', used to evade or attenuate injustices or to undermine otherwise unassailable power holders" [26]. In this regard, a recent study carried out in Italy showed that among migrants distress due to post-migratory liv-

ing difficulties amplified the tendency to somatisation [27]. In a cross-cultural perspective, this evidence shows the phenomenological centrality of the bodily experience, "which may often become the primary or only channel of communication in a migratory context"[24]. However, a number of studies do not support the suggestion that misdiagnosis can explain these high rates. For example, in the UK AESOP study diagnostic changes following a first episode were not more evident in black minority groups [28]. Moreover, there were no marked differences in clinical profiles [29], a finding that mirrors what Harrison et al. [30] found in Nottingham. Finally, one of the few studies to directly assess diagnostic bias found no evidence of misdiagnosis in ethnic minority patients [31].

The impact of social regulation of human gene expression

The results of these studies show that the period of migration, or the migration process itself, may confer an increased risk for schizophrenia and other psychoses regardless of whether the parents are foreign-born or natives. Some studies have addressed whether the high rates found in migrants could be due to higher genetic or biological vulnerabilities: no evidence was found. Two studies conducted using the AESOP sample investigated minor physical anomalies [32] and neurological abnormalities [33] across ethnic groups and found no differences. Furthermore, greater differences in brain structure, such as reduced global grey matter and increased gyros grey matter, were detected between black patients and black controls than between white patients and white controls [34]. The authors, however, concluded that explaining these findings is at best speculative because they could be related to exposure to earlier neurological insults, but they could also be the consequence of greater exposure to adversities and trauma or to exposure to antipsychotics (notably, the current dosage of antipsychotic medications was significantly higher in the black Caribbean and black African patients). A study conducted in Netherlands [35] addressed the problem of migrants' genetic predisposition to psychosis. The authors administered the *Family Interview for Genetic Studies* to a sample of Morocco migrants and Dutch natives FEP patients and found that age and sex-adjusted risk for non-affective psychotic disorders (NAPD) were similar in both parent groups. However, among siblings, the adjusted risk for NAPD was significantly higher in the Moroccan-Dutch group than in the Dutch group. The authors concluded that their results suggest that environmental factors in the Netherlands have a greater impact on the psychosis risk for male immigrants from Morocco.

In addition, recent analyses have highlighted that social factors can represent environmental risk factors because they might regulate gene expression. Facing severe or chronic stress [36] such as social isolation, low socio-economic status, late-life social adversity may result in long-term, sometimes permanent, alterations of the biological stress response system may take place [37].

A role of primary importance is played by the hypothalamic pituitary-adrenal (HPA) axis and its final product, glucocorticoid hormones [38]. The activation of the glucocorticoid receptor inhibits the transcription of many immune response genes via suppressive binding of the glucocorticoid receptor to gene promoter sequences, glucocorticoid receptor-mediated transcriptional induction of anti-inflammatory genes and non-genomic antagonism of pro-inflammatory transcription factors [39]. HPA axis alterations indicative of low cortisol, increased glucocorticoid sensitivity and functional desensitisation of the glucocorticoid receptor have been demonstrated in severely stressed adults [40]. Additional insights into the immunological effects of long-term social stress have come from transcriptional profiling of circulating leukocytes in human population [41]. People confronting long-term social adversities such as extended periods of stress [40], threat and social isolation have repeatedly been found increased expression of pro-inflammatory immune response genes with elevated circulating levels of IL-6, IL-1β and IL-8 and decreased expression of genes involved in INF antiviral responses [42]. This pattern of pro-inflammatory/antiviral transcriptome skewing has also been observed in experimental animal models of social instability [43]. Although it is well demonstrated that this biological pattern can promote inflammation-related cardiovascular, metabolic, neurodegenerative and neoplastic diseases [44], more extensive social genomics studies are necessary to define the possible impact on vulnerability to mental disorders, such as psychosis. Interestingly, a recent meta-analysis suggests the presence of an inflammatory syndrome in schizophrenia [45]. Finally, epigenetic mechanisms can provide another pathway by which social environmental might regulate gene expression: human studies have documented associations between DNA methylation profiles and socio-enviromental risk factors such as low socio-economic status and childhood stress exposure [46].

Since migration is an important stressful life event, and difficulties in integration in host countries may remain chronic, this can be conceptualised within the vulnerability stress model of risk for psychosis. Although individual risk is still considered to be mediated through susceptibility, the biological evidence highlights the importance of social regulation of the expression of human genes. This raises new conceptual questions, such as, "What role does host-culture or social isolation or migration process play in modulating gene expression in migrants?", "What is their impact on vulnerability?".

Discussion

The reviewed studies covering a period of more than 30 years and highlight the history of migration in all its dimensions (personal or parental; current or past) and the role of minority status in increasing the risk of psychosis. Clinical studies add the important insight that psychopathological differences and misdiagnosis do not explain the excess of psychosis found in migrants and ethnic minorities. Most studies reveal different levels of risk depending on the minority with different geographical origin. It is interesting to note that the origin group at risk for psychosis varies in different countries [3]. This may indicate that socio-environmental risk factors faced by origin groups operate differently in different countries, depending on social experience and available resources to cope with adversities. Considering the relevance of migration in Western countries, primary epidemiological studies should be carried out to identify in each context the most vulnerable minority groups and to implement targeted prevention interventions.

The risk factor most commonly investigated and with a certain level of cross-cultural consistency is ethnic density: in both UK and Netherlands, the risk of psychosis is higher in minorities who live in areas with low ethnic density and who are exposed to conditions of low social capital and greater isolation. Interestingly, this risk factor at the area level corresponds to an individual risk factor, strong cultural identity, and to a family risk factor, dual foreign born parentage, as a dimension which exacerbates the distance between minorities and majorities [10 16]. It is possible to hypothesise that low ethnic density at the area level, dual foreign born parentage at the familial level and strong cultural identity at the individual level are proxies for social isolation of minorities. Social isolation can lead to dopaminergic dysfunctions and thus increase the risk of psychosis.

Other social and psychological risk factors in minorities include the social disadvantages and discrimination [8] and the "mismatch" between expectations and achievements [10]. With regard to migrants, younger age at the time of migration predicts a higher risk for psychotic disorders, and there is evidence that selective migration cannot explain the higher risk found among migrants [15]. Moreover, the risk associated with migration may accumulate over time [14]. From studies conducted in Italy, we know that recent first-generation migrants are also at higher risk of developing psychosis [17 18]. These findings could suggest a lower degree of biological vulnerability and, perhaps, a higher burden of psychosocial disadvantages in migrants and minorities compared to natives, confirming the socio-developmental pathway to psychosis proposed by Morgan et al. [8], who suggested that the high rates of psychosis are largely social in origin. Following the gene and environment interaction model, these social factors could interplay with the regulation of gene expression in the onset of psychosis. The results of the EU-GEI study [48], a Europe-wide incidence and case–control study of psychosis conducted in 12 centres chosen to include areas with large first and subsequent generation migrant populations, will give us the opportunity to directly test components of this model.

Conclusions

In conclusion, misdiagnosis as the cause of the excess of psychosis found in minorities and migrants seems to be ruled out by the available evidence, and several psychopathological follow-up studies have shown that psychosis diagnosis is consistent over time [28]. In addition, there is evidence that the quality of health and psychosocial care for migrants may be affected by barriers to psychiatric care access, such as administrative structures, linguistic and communicative skills, cultural distance and the mismatch between users' health-care expectations and those of healthcare providers.

The current literature shows that the migration experience as well as the minority status are risk factors for psychosis. As Morgan & Hutchinson argued in 2009 [49], this is a public health tragedy, and one that remains neglected. This tragedy could be at least attenuated by several psychosocial interventions, targeted at social disadvantages and at those individuals and populations who are at highest risk [50].

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Psychopathology in postmodern societies

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Summary

Objectives
A growing body of evidence suggests that postmodern societies currently face a significant number of changes imprinted by evolution at a number of levels. These changes are resulting in increasing stress both at the population and individual levels, possibly leading to mental health problems. Many social variables are subject to rapid fluctuations which, in turn, affect changes in society leading to mental health consequences of the population. In this paper we review the available literature on social variables subject to rapid changes in postmodern societies with links to the DSM-5.

Methods
Search of papers until June 2015 was carried out using PubMed. We considered only on variables that can be identified in societal changes from modernity to postmodernity and that cause stress, mental distress and mental disorders.

Results
Discomfort is present in situations where the subject experiences feelings of subjective malaise, beyond the presence of biomedical symptoms. Mental disorders are strongly linked with situations such as technology, markets, economic forces, environmental crises, pollution, demographic crisis and cultures in the building process, including their manipulation.

Conclusions
The review confirms the psychogenic psychological problems and uneasiness connected to crises that post-modern society creates within communities and environments.The DSM-5 offers a potential explanation to the social variance related to psychopathology.

Key words
Postmodernity • Systemic Risks • Crises • Psychogenic disorders • Flux and psychopathology • Short/long term consequences

Introduction

Generally, the term "postmodernism" refers to the contemporary culture that is replacing industrial cultures, designed by the Bretton Woods system after WWII. Postmodernity, therefore, is an economic or cultural state or condition, although its limits are seen as variable and controversial. As a result, the notion of controlled progress has been replaced by high-risk progress [1]. Postmodernity includes at least three phases. The first is combined with post-colonialism and becomes post-capitalism. This process is still ongoing, and is added to the second phase – or neogenesis – in which new social processes, which are quite unexpected and may be improvised, come forth in the form of crisis, flows, transformation, assembly, metamorphosis and mutation. These processes are apparent at all levels and include communication, flow of ideas and reorganisation of power. The third phase is that of synthesis, which is represented by a reorganisation within legal parameters, ethical relations and safety standards.

At present, postmodern culture is globalised by technology, defined by mechanical reproduction of goods, with the beginnings of information theory, and the liquefaction of the political blocks [2]. The organisation of values is based on the free market, neogenesis phenomena, loss of the value of knowledge in terms of its consumption [3], changes in the conception of the mankind [4], work on social simulacra [5] and the permanence of the state of crisis in the bio-psycho-social paradigm [6]. Societies have always had their own dynamics and, as any other system, also have a maximum load. Within the range of sublevels of a society, individuals can maintain identity and purpose of a common action. After reaching the maximum load, the social system goes into an emergency or a phase change. The previous balance will not return. Regardless of how this systemic crisis occurs, the redistribution of forces will involve most of the substructures that were previously found within a certain balance. It is therefore obvious that some substructures will not survive, whereas

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others will be transformed. When a crisis affects a social system, it is often difficult to recognise the end of a period and the beginning of a new one with new structures. In this scenario, the study of psychic phenomena becomes complex. For example, two phenomena apparently related to mechanisms of cause and effect could instead be the product of a third constant interference, something that is not yet known; or observed psychic dynamics may be part of a broad automatic change, so slow that it cannot be caught on the basis of extemporary aspects – a sort of change in the system, a period of fluctuation, an algorithm, a decrease of energy or subtraction of mass in the system. This can be illustrated by the impact of climate change [7]. Social psychiatry states that there are systems related to culture [8], languages and laws. Academics in social neuroscience are studying the action of these factors, due to the fact that the focus was previously on one type of neurogenetic approach. Today, this single approach is no longer sustainable. Neuroscience has to anchor top-down methods of investigation (social/encultured) as well as bottom-up (neuro-evolutionary perspectives) [9 10] in order to build a working model. Postmodernity is replacing modernity with great speed compared to other previous historical transitions. The speed is related to the impact of social media and globalisation as a whole. Even the speed of urbanisation has been astonishing. Given the speed, many structures, buildings, relationship dynamics have maintained a certain aesthetic form of modernity. Postmodernity generates "postmodern personalities". Within this context, psychopathology steps in, following social transformations, reflecting the manner in which psychiatric disorders embody this complexity. The forces that are pushing the transformation from modernity to postmodernity are mostly related to "flow and flux" of material changes and resulting stress. The influence on psychopathology is due to new stressors on vulnerable groups and individuals, or to changing realities. The susceptibility of groups or individuals depends on the context or reality within which groups and individuals live and work. When these settings become fragile, inhospitable, or with a lack of emotional resources, that is when psychopathology can emerge.

Materials and methods

There are several methodological problems to consider when assessing the effects of social variables on mental health. The first is how social variables are defined. Although one can discuss the validity of the definition of this term, most authors agree that social variables can be measured. The goal is to identify social conditions that cause a detrimental effect on the mental health of populations. Psychiatric disorders can be divided into three categories according to their main cause: psychogenic disorders, endogenous disorders and exogenous disturbances. Psychogenic disorders are a result of stress, shock, psychological traumas in childhood, adolescence or adulthood – in this case they are short or long-term consequences of social changes. While it is easy to identify a direct relationship of immediate cause and effect, significant long-term effects are harder to understand. Long-term consequences are generally divided in: 1) effects on the person directly exposed to stress after some years; 2) effects of stress on family, extending beyond childhood and into adulthood; 3) effects of stress transmitted to subsequent generations through culture; 4) effects of stress transmitted to subsequent generations through mutations. An example of such an approach is that recently proposed by the WHO work on a PTSD risk algorithm, where PTSD may be predicted and prevented [11]. A second methodological problem is how to measure mental health although different ways, such as surveys on mental disorders/suicidal thoughts in primary or secondary care settings, have been developed. For example, with regard to the economic crisis, Rihmer et al. [12] looked at annual antidepressant consumption, which can be seen a possible proxy for the availability of psychiatric services and the treatment of depression, which is the most powerful predictor of suicide at the individual level.

Results

Technology

In the last 30 years, technology has far exceeded growth expectations, leading to an acceleration in all fields of knowledge, and to the obsolescence of previous understanding and know-how [13]. Technology is the basis of post-modernism and information-age capitalism. It has been suggested that the discipline of psychology should consider whether technology is able to change the characteristics of the ego and the self [14 15]. There is no doubt that the use of Internet by children and adolescents and its impact on the development of identity (identity exploration) [16] is critical, but we still do not know about the long-term effects of this use. However, it is not clear if the technology makes the users' traits and personality truly visible [17], creating new forms of adaptations or dysfunctions that would not exist without technology. The use of websites like *Parallel Lives*, where individuals can change their identities and choose to be whoever they want, raises interesting ethical dilemmas. Currently, pathological gambling is the only behavioural addiction included in the DSM-5. Preliminary evidence from positron emission tomography imaging studies suggests that a general "Internet addiction" can lead to brain changes which are similar to those associated with substance use disorders,

including changes in glucose metabolism and dopamine levels in brain areas that are associated with substance abuse [18]. New syndromes and disorders related to the use of Internet, including cyberchondria, cyberbullying, cybersuicide, cybersex and pathological video gaming are arising [19]. There is no doubt that many other forms of social media addictions are waiting to be discovered. More detailed investigation is needed to understand the effect that technology is having on those who are vulnerable (cybershopping, cybergambling, smartphone addiction, recruitment for terrorism [20]) and now these factors can change identities.

Markets and their impact

With increased and rapid globalisation, markets have become much closer than they were and have taken the characteristic of "prosumers", i.e. registering and offering products that consumers themselves contribute to describe and demand. Consequently, the market changes and tends to take a role which dictates demands. In fact, the intake of illegal drugs is typically associated with the imbalance of a range of neurotransmitter pathways/receptors, and consequently with the risk of psychopathological disturbances [21], and certain behaviours are based on genetic vulnerability ('reward deficiency' in the nucleus accumbens, impulsivity and tendency to develop craving). The market, meanwhile, tends to evoke similar stimuli because they have been studied in the brains of employees and requested by consumers themselves. Illegal drugs are produced and circulated on the Internet faster than we can study or define them [22], while on the other hand they are undergoing a process of legalisation with a renewed availability and tendency to be abused. The similarities between drug abuse and the automobile market may be farfetched, but both produce effects on individuals. Products in the market (clothing, tourism, media) are generated not only following the desire of consumers, but also trying to modify their desires. The postmodernity market follows what we know about addiction: the market tends to make consumers "dependent" on the products, especially designer products, which may be over-priced, trying to leverage trends that are usually temporary [23]. Increasingly online suppliers are using algorithms to explore consumers' preferences. In this way, we can observe epigenetic changes, with predisposing consumers (since childhood) to excessive purchase. For example, the early use of alcohol in teens seems to follow this pattern of epigenetic-cultural stimulus progressive: alterations in brain circuitry that follow excessive drinking, by disrupting executive function, and making it harder to stop [24].

Economic forces

Some social and economic trends expand on the planet aiming to hoard resources, speculation and transformation of the wealth of energy flow (e.g., cash flow), where local populations may receive absolutely no benefit. The consequences of this type of action are the development of crises, as well as the impoverishment of people and nations. Various forms of economic crises are interconnected with depression [25], psychosomatic symptoms and somatoform disorders, increased rates of alcohol and drug abuse, violence [26] and suicide [27 28]. In the European Union, rising unemployment rates have been shown to be associated with significant short-term increases in premature deaths from intentional violence, including suicides [29]. Increased levels of stress or depression are found to be important indirect causes of the increase in mortality observed during periods of economic crisis [30]. The association between psychopathology and poverty has been repeatedly demonstrated in culturally diverse cases and constantly over time [31]. Developing countries, especially those in "extreme poverty", are badly hit by economic crises [32]. The effects of poverty, especially on children, may in fact be even greater than suggested [33]. Protective actions to combat economic exclusion and promote social participation of individuals with mental health problems are even more important during times of economic crises [34]. Social inequalities cause mental and physical illnesses and, with recent trends of economic downturn, an increase in mental disorders in many countries has been observed.

Environmental factors

The planet is changing and the impact of environmental change is considerable. The increase in temperature, drought, lack of water and pollution affects the mental health for the groups affected by exodus and wars, as well as territorial and geopolitical instability. Current research is discovering how the production of waste created in the postmodern society influence brain connectome. Environmental disasters are a serious concern for pollution. The effects of urban normal and exceptional levels of pollutants on the brain are under exploration. Car pollution (polycyclic aromatic hydrocarbons PAHs) can contribute to the development of behavioural problems, such as attention-deficit/hyperactivity disorder (ADHD). Ionising radiation has effects on the brain and leads to the development of psychopathology – studies began with research on the Chernobyl disaster [35 36] and continue today with the tsunami and disaster in Fukushima [37 38]. The psychopathological effects of ionisation, such as PTSD, mood and anxiety disorders, is connected to risk perception, fear of radiation, evacuation and displacement [39]. Urbanisation appears to be the environment of choice for the human being, and at the same time the site for environmental crisis. Living in urban areas, and therefore urbanisation itself, has been included among the eight

major environmental risk factors for schizophrenia, together with cannabis, migration (and ethnic density), obstetric complications, birth timing, infectious agents (and inflammatory responses), socio-demographic factors and childhood trauma [40]. People living in urban areas have a higher incidence rate of psychopathology than those from rural areas or "green" or environmentally friendly urban areas [41 42].

Changing demographics

Demographics are significantly changing in post-modernity due to several factors, such as reduced birth rates, population ageing and migration. Migration, in particular, requires a pediod of adaptation to incertainty. In postmodernity, migration continues to evolve in parallel with geopolitical and ecological crises, as well as globalisation. It is estimated that nearly 200 million people live outside their country of birth (for economic reasons, to escape war, persecution or natural disasters). In itself, migration does not constitute a hardship or a challenge, however it is a crisis in which many social variables are redistributed and changed [43 44]. The process of migration exposes individuals and groups to stress and to the possibility of developing mental disorders [45 46]. Migratory stress depends on the manner in which each individual initiative before and after migration takes place, their subsequent failure or success, the interaction between cultures of origin and arrival, as well as the integration of first and later generations of migrants [47]. With regard to displacement, it is quite different when people move alone or in groups, voluntarily or involuntarily, or whether they have a plan and a good level of security. Social class, ethnicity, gender and age are systems that embody the different distribution of resources and opportunities: a low social status and the lack of possibility regarding mobility (trapped within pockets of poverty) may already be a factor stress [48 49]. Therefore, stressors related to migration may be the inevitable outcome of systematic discrimination and social injustice. During integration processes, the gap between the culture of origin and the host culture can produce social isolation, stress, lower quality of life and suicide [50].

The cultures of the future

The DSM-5 indicates that ethnicity and race are points of strength and endurance for a group, but can lead to psychological interpersonal or intergenerational conflicts [51]. Cultural groups show both resilience and fragility aspects that are crucial in determining the success or failure in overcoming adversities in the integration process. Trends show that today's societies are more heterogeneous and are not linked to ethnicity. It would appear that individuals and communities are increasingly characterised by the possibility of access to resources and by the ability to move to another part of globalisation. Local contexts, characterised by social immobility, poverty, marginalisation and closure, will be possible reservoirs of future psychopathologies. Living in critical conditions, such as poverty, domestic violence and exposure to generic risks is associated with higher levels of stress that have noteworthy repercussions on mental health. Studies have found that people who are trapped in ghettos and slums [52] with future concerns or immigration centres are at risk for developing new forms of mental disorders, according to their situation [53]. The same is true for those who live in war-torn countries or regions [54], as well as in conditions of repression, political instability, or terrorism. People in these conditions unsuccessfully support stress and are less resilient, and show higher levels of stress, anxiety and depression [55]. It is well known that losing a close family member, such as a parent, sibling or spouse, is a source of great distress [56 57]. In addition, death and severe physical illness of a family member along with financial difficulties, violence and interpersonal conflicts are strong predictors of future health problems, such as anxiety and drug abuse. Internally displaced persons are forced to flee or to leave their homes or places of usual residence, particularly in order to avoid the effects of armed conflict, situations of generalised violence, violations of human rights and natural or man-made disasters [58-62]. According to the *United Nations High Commission for Refugees*, internally displaced persons are those who are forced to flee, but either cannot or do not wish to cross national borders [59]. A meta-analysis of studies published from 1962-2004 highlighted the impact of internal armed conflict on the prevalence of mental disorders [60]. Moreover, the culture of countries with moderate income and stable democracies is changing. This is particularly evident in the way groups come together, paired with changes with regard to family, individuals and cultural values. Postmodernity is defined by this trans-evaluation of values, leading to the birth of what can be defined as an egocentric, transgressive (hence risk taking) and postmodern personality [62]. Recent or new cultures are one of the major factors for recognition of symptoms and, consequently, for the interpretation of experiences of stress [63]. During crises, the effect of social changes on psychotic disorders (hallucinations, delusions, depersonalisation) [9], social withdrawal [64] and violence to self or others has been shown. Finally, the culture of psychiatry itself can be influenced by a number of factors, including the interest of the market and the deviations of psychopathology. The first aspect deals with the culture of the technology market that generates a reversal in rank and role between science and technology, downgrading science and upgrading technology. This setting is a marker of the transition from modernity to postmodernity. It is a

type of displacement of the methodical, disinterested scientist: the ideal scholar of modernity [65]. The other aspect regards contrived behaviour and imitation [66]. DSM-5 has been recognised and included the category in *Other conditions that may be a focus of clinical attention* [51] (DSM-5, 2015). The fundamental characteristics of the mimicking and imitation are: 1) presence of individual symptoms, unconnected and free of pathological correlation; 2) production, display and listing of these symptoms; 3) lack of emotional participation by those who show them. The criteria for making a diagnosis are: 1) the absence of clear signs of illness or personality disorders; 2) awareness of what is being done and the motivation that determines how they are imitated; 3) clarity of purpose to achieve. Imitation is a mechanism that is not widespread in the general population [68]. It occurs almost exclusively in forensic psychiatry as a defence in criminal matters [69]. It is aimed at achieving subsequent benefits when undergoing expert evaluation for purposes of judicial proceedings, awards or compensation for a disease pertaining to retirement benefits. Recognising imitation or mimicking is quite challenging in many cases, since patients who are already suffering from mental disorders tend to accentuate existing symptoms. More often, the presence of psychiatric diagnoses has been used to explain criminal behaviours or avoid harsh prison sentences [69]. The issue of mimicking and imitation in postmodernity raises a number of questions. The nature of clinical disorders observed in special environments and resulting in ethical aspects, as well as the response of the concerned authorities, are worth exploring further. We should consider problems which become actualised in postmodern societies. *Psychologism* and disease mongering for example proceeds by 3 steps: 1) the genralised tendency to interpret events or arguments in psychological terms; 2) the attention of mass-media, with the result of an increase in the awareness about knowledge of definition and treatment methods for several prychiatric disorders; 3) the number of patients who have the diagnosis actually increase [70 71]. Among all fields of clinical medicine, psychiatry is undoubtedly the most vulnerable to the danger of disease mongering; for example, the number of patients with depression in the countries where SSRIs were marketed significantly increased. This contract with society is critical in funding mental health services and in managing social expectations from psychiatrists. Contexts such as assisted suicide of psychiatric patients [72] and clinical assessment during media-driven cases or proceedings [73] can significantly influence psychiatric cases in a scenario that changes quickly.

Emerging models in the DSM-5

Since the DSM-IV was first published, we have seen a remarkable progress in the field of neuroscience, genetics, and social and human sciences [51]. Although the bio-psycho-social model has been well theorised and accepted, its application in diagnostic systems remains uncertain [74 75]. The DSM-5 task force had to find a balance between the newer advances and the older categorical classifications: it has been recognised that an excessively rigid categorical system does not properly describe all clinical aspects or symptoms that may occur in different disorders that are fluid over time [51]. Moreover, new diagnoses and disorder subtypes/specifications have been considered, and many clinical conditions, subjected to additional demonstration regarding their reliability, have been included in the *Conditions for Further Study* in Section III of the manual. In addition, the DSM-5 deals with other factors such as cultural and social-related conditions, as well as relational, educational, occupational and housing issues, which include economic problems or problems related to access to medical healthcare which may affect diagnosis, course of illness, prognosis and treatment of mental disorders [51]. *Other conditions that may be a focus of clinical attention* has been extended in the new edition of DSM-5 including problems related to family upbringing, problems related to primary support group, child/adult maltreatment and neglect, as well as educational, occupational, housing and economic problems. Interestingly, problems related to social environments are listed referring to the migratory condition and its related aspects [51]. Moreover, psychiatric home treatments may be suitable, but can be effective only if individuals and their careers have secure addresses, and the patient can be approached and treated [76]. Secondly, psychiatric disorders may themselves lead to homelessness, and homelessness leads to mental illness in a circular and vicious manner [77]. In fact, the DSM-5 brings attention to problems related to homelessness or inadequate housing/economic conditions, including extreme poverty and insufficient social insurance or welfare support. Many studies show a 5-6 fold increase in the mortality rate among homeless patients and higher cognitive impairment only partially due to the psychiatric condition [78]. International groups, in particular the European Psychiatric Association, aim to address social factors that may lead to homelessness [79]. The *Other conditions that may be a focus of clinical attention* section includes some categories focused on the different phases of life, as well as problems related to living alone, acculturation social exclusion or rejection, and discrimination or persecution. These conditions reflect the impact of social environments on the individual's diagnosis, treatment and prognosis, especially for people involved in migration, who are more likely to be (or have already been) exposed to trauma. This section also sheds light on spiritual problems, unwanted pregnancies, victims of terrorism or torture, problems related to access to

medical healthcare and all problems connected to social determinants of patients. These new categories confirm the attention of the international groups and societies in considering mental illness within the full framework of the bio-psychosocial model [80]. Section III of the DSM-5 provides a list of proposed disorders for future study and a comprehensive review of the cultural context of mental disorders. Proposed models include personality impairments as well as pathological personality traits, attenuated psychosis syndrome and non-suicidal self-injury, all relevant and frequent clinical conditions that still need more evidence for approval. We should also note that the current manual recognises how the cultural context of illness may be essential for an effective diagnostic assessment and clinical management [51]. The DSM-5 provides a framework for assessing information about cultural features of patients and their mental health problems. The DSM-5 deals with some constructed categories of identity such as *race* and *ethnicity*, which are involved in the aetiopathogenesis of mental health problems [77]. The outline for cultural formulation includes cultural identity of the individual, cultural conceptualisations of distress, psychosocial stressors and cultural features of vulnerability and resilience, cultural aspects of the relationship between the individual and the clinician, and overall cultural assessment. Cultural syndromes are clustered in groups, communities or contexts, and are recognised locally as coherent patterns of experience [51]. Cultural idioms of distress are ways of expressing distress that may not involve specific syndromes, but provide collective experiences and concerns. Cultural explanations or perceived causes are labels, attributions, features of an explanatory model that indicate culturally recognized aetiology for illness [51]. Among new conditions "for further study", the DSM-5 focuses on Internet gaming disorder as a significant public health relevant disorder. The DSM-5 has also revised the concept of traumatic events and related criteria for PTSD, which has been included in a new chapter on Trauma- and Stressor-related disorders. The trigger for PTSD is identified as an exposure to actual or threatened death, serious injury, or sexual violation. Indirect exposure is defined more specifically as "learning that the traumatic event occurred to a close family member or close friend", and "actual or threatened death must have been violent or accidental" [51]. The following changes have been made in the DSM-5: 1) PTSD has been moved from the group of "anxiety disorders" to the new category of "Trauma and stressor-related disorders"; 2) the traumatic event has been redefined and, as such, may create ambiguities and problems of interpretation; and 3) the symptom clusters have been changed, with the addition of more symptoms – negative beliefs/expectations, distorted blame, persistent negative emotions, reckless or self-destructive behaviour, and a dissociative subtype has been added [51]. Recent research in neuroscience suggests that the malleability of memory and the process of reconsolidation improve the body's ability to respond to new or unforeseen emergencies – this is a complex but promising field of research in PTSD, which may lead to more effective and culturally appropriate therapeutic intervention, aimed at interfering or block the reconsolidation process [79]. However, the traumatic event itself does not sufficiently explain why the disorder develops or persists with time passing [79]. Risk factors may be related to the traumatic event or to the person experiencing the event (i.e. gender, educational level, previous traumatic experiences, child abuse, etc.) [79]. Moreover, studies among war-torn populations have shown that repeated exposure to trauma is cumulative, rendering a person more vulnerable to the development of PTSD: they found a linear decrease in mental health and social performances proportional to the increase in traumatic events [79]. The way that social and cultural factors may affect mental syndromes and disorders, and therefore their outcomes, deals with the concept of "pathoplasticity". The principles supporting this theoretical model include an examination of cultural factors on an individual's personality, while suggesting tailored treatments based on an assessment of pathoplastic models [79].

Conclusions

The current literature supports the belief that cultures in transition rapidly produce a quantity of spurious social variables that influence coping skills of groups and individuals. It is clear that the uncomfortable living conditions generated by the structure of globalisation are responsible for a great deal of exogenous psychopathology. Several authors are discussing new syndromes, while others believe that the crisis of postmodernity simply shed light on already discussed mental health conditions, paired with different resilience. In any case, many parameters of this ecosystem are changing. It is now believed that crises, as well as tools and processes that allow us to fight extinction (resilience), are part of the production of the same complexity that drives the multi-level (eco)systems. A place is vulnerable when it is hit by variance (variables) that affect social stability – an individual is vulnerable when he/she is sick, with alcohol and/or drug addiction, with poor access to resources, lack of proper information, difficulty of movement, lack of democracy (deficit of rights), contact with pollutants, or when living in areas with geopolitical crisis (political gap). The aetiology and clinical picture of the developing psychopathology has started to change. These changes are reflected in the psychopathology of children and adolescents, which may

have certain dynamics corresponding to changing social factors such as social media, economic downturn, etc. Thus, it is important to address the question of quality of the emotional family environment in which the child is growing up [81]. Moreover, it appears that certain types of PTSD may last for one's entire life, even traversing across generations and disrupting social attachments and adaptations. The analyses of changing paradigms should be the goal of research in the field of social neuroscience. Psychiatry provides fundamental knowledge, tools and studies that are now solidly established and continuously renewed. This field of studiy provides an important view on how the culture of groups can cause new pathologies and modify psychopathological symptoms.

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