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GIORNALE DI PSICOPATOLOGIA

Editor-in-chief: Alessandro Rossi

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Kaplan HI, Sadock BJ. *Comprehensive textbook of Psychiatry.* Baltimore: Williams & Wilkins 1985.
Chapters from books or material from conference proceedings:
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Post-traumatic stress disorder in the DSM-5

Il disturbo post-traumatico da stress nel DSM-5

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the *American Psychiatric Association* (APA), published last may, brought several changes to current psychiatric classifications. An interesting category that will be subject to change is Anxiety Disorders. Obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) will now form two new categories together with related disorders currently placed in other categories: *Obsessive-Compulsive and Related Disorders* and *Trauma and Stressor Related Disorders*, respectively.

PTSD had well-characterized diagnostic criteria starting with the DSM-III (APA, 1980) as a consequence of dramatic evidence of psychic pathologies that, almost epidemic in proportion, manifested in veterans of the Vietnam War: previously, the literature described syndromes related to a variety of traumatic events (prisoner of war syndrome, sexual abuse, battered women, etc.). The numerous studies on clinical characteristics, epidemiology and neurobiology, carried out on Vietnam War veterans, and later in other groups of subjects exposed to other types of traumatic events (physical and sexual violence, concentration camps, etc.), led to the first diagnostic description of PTSD. Following this, epidemiological studies were carried out in several countries, which indicated that the lifetime prevalence of PTSD was around 10.1% [1]. This was also extended to studies on victims of mass trauma, such as terrorist attacks – firstly 9/11 in New York [2] – and natural disasters such as earthquakes [3].

These studies have taken into account not only risk factors, resilience and course of disease, but also the complications of PTSD as well as the subclinical and partial forms, which are neither less relevant or invalidating than the syndrome with complete symptomology [5-8]. This emphasizes the fact that PTSD is characterized not only by a high risk of suicidal and abusive behaviour, but also by other maladaptive behaviours (e.g. dangerous driving, aggressive or self-destructive behaviour, at-risk sexual encounters), which some believe to be the core elements of PTSD [9-11].

The large amount of data collected has fuelled debate about the need for better diagnostic criteria. On the basis of numerous investigations during the last 20 years, the workgroup for *Anxiety, Obsessive-Compulsive Spectrum, Posttraumatic, and Dissociative Disorders* of the task force for the DSM-5 proposed to exclude PTSD from the section on Anxiety Disorders, and to create a new section on Trauma and Stress Related Disorders. According to the task force, the latter should include all those disturbances whose aetiopathogenesis is correlated with a traumatic event, and to modify the current diagnostic criteria (DSM-IV-TR, 2000). In particular, Criterion A, relative to the traumatic event has changed, together with symptomatological criteria, that have been increased from 3 to 4.

A new section: Trauma and Stressor Related Disorders

The placement of PTSD within the section on Anxiety Disorders, such as OCD, was somewhat criticized. As a result, the workgroup felt that such criticisms could be addressed by creating two new sections on *Obsessive-Compulsive and Related Disorders* and *Trauma and Stressor Related Disorders*. This latter includes disturbances that have their aetiopathology in a stressful traumatic event, which represents an essential factor in determining the disorder, and is thus a key element that displays an entire spectrum of psychopathological reactions to environmental stress factors. In fact, in addition to PTSD, 5 new categories have been added: *Reactive Attachment Disorder, Disinhibited Social Engagement Disorder, Acute Stress Disorder, Other Specified Trauma and Stressor Related Disorder.*

Diagnostic criteria of PTSD

The traumatic event

The definition of a traumatic event (Criterion A), necessary to formulate a diagnosis of PTSD, has evolved over time. In its first definition in DSM-III (1980), Criterion A foresaw exposition to *"a recognizable stressful event that would provoke significant symptoms of illness in almost*

all individuals". Later, in the DSM-III-R (1987), this criterion was the object of a reformulation aimed at clarifying the original definition, adding that the traumatic experience had to be *"outside of the usual human experience"*. However, in the attempt to provide typical examples of stressful events, the manual included potential stressors that were not outside of the normal human experience, such as being the victim of a criminal act or being involved in an accident. With the DSM-IV (1994), this criterion was subjected to an additional evolution: the connotation *"would provoke significant symptoms of illness in almost all individuals"* was eliminated, and Criterion A was subdivided in two components, one objective (Criterion A1) and one subjective (Criterion A2). For the first, *"the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others"*; for Criterion A2, *"the person's response involved intense fear, helplessness, or horror"*. This division had the aim of balancing the risk of an excess number of diagnoses due to the non-specific nature of Criterion A1, and increasing diagnostic specificity with the introduction of Criterion A2 for the subject's intense emotive reaction.

In reality, epidemiological studies have demonstrated that *"intense fear, sentiments of impotence, or horror",* if not present in the immediacy of exposition to the trauma, moderately reduce the estimated prevalence of PTSD; if present, they are weak predictors of PTSD at 6 months compared to other post-traumatic emotive reactions, such as anger or shame. Moreover, some authors have highlighted the risk of recall bias in the evaluation of Criterion A2: cases of PTSD are often evaluated months or even years after the traumatic event, thus implying a retrospective evaluation of Criterion A2, which is influenced by the current psychopathological state of the patient.

Considering this, the task force of the DSM-5 changed Criteria A1 and A2 into a single Criterion A with the aim of eliminating the existing ambiguity and adopting a restrictive approach for the selection of traumatic events. In recent years, in fact, among PTSD experts two points of view have formed. One sustains the importance of including low magnitude traumatic events, such as divorce, physical illness, bankruptcy, abortion, continuous or recurrent stress. The other underlines the importance of more restrictive definitions to avoid the risk of excessive subjectivity. The DSM-5 has opted for the second hypothesis, favouring more restrictive criteria.

The new Criterion A [a] foresees, in fact, the actual exposition to, or threat of, death, severe injury or sexual violence, which may be either direct through personal experience; direct testimony of a traumatic event occurring to others; become aware that the victim of a traumatic event is a family member or close friend (whose death, real or threatened, must have been violent or accidental); the repeated experience or exposure to extreme repulsive details of a traumatic event (as in the case of emergency services for the collection of human remains; police officers repeatedly exposed to details of child abuse), but with the specification that this condition does not apply to exposure via electronic instruments, television, movies or photographs, unless it is linked to work activity.

Symptomatological criteria

The DSM-IV-TR foresaw, for a diagnosis of PTSD, the presence of a symptomatological triad that included: re-experiencing (Criterion B), avoidance or emotional blunting (Criterion C) and an increase in arousal (Criterion D). The validity of this structure based on these three symptomatological clusters was investigated in numerous studies, based on factorial analyses, that allowed for the identification of models with two, three or four factors. These studies suffered from methodological limitations since different instruments for evaluation were used in cohorts of patients with PTSD who experienced different levels of trauma. However, the majority appeared to support the four-factor model in which re-experiencing, avoidance and hyperarousal retain their identity, while the fourth factor appears less well defined.

Several studies indicated a fourth factor, emotional blunting, characterized by symptoms included in DSM-IV Criterion C (avoidance) and numbing, while a small percentage indicated dysphoria, which is considered a combination of a relative emotional blunting and symptoms of hyperarousal also associated with depression. Both hypotheses demonstrated to be valid, with a slight advantage favouring dysphoria as a fourth factor. However, the task force chose emotional blunting for the pos-

[a] Exposure to actual or threatened a) death, b) serious injury, or c) sexual violation, in one or more of the following ways:
1. directly experiencing the traumatic event(s);
2. witnessing, in person, the traumatic event(s) as they occurred to others;
3. learning that the traumatic event(s) occurred to a close family member or close friend; cases of actual or threatened death must have been violent or accidental;
4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse); this does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work-related.

sible overlap of symptoms of PTSD associated with the dysphoria factor and similar ones that are observed in other disturbances that are often comorbid, such as depression or anxiety disorders. In the DSM-5, therefore, the symptomatological structure of PTSD has gone from three to four criteria. The fourth criterion has been named *Negative alterations in cognition and mood*, which derives from the separation of some of the symptoms formerly present in Criterion C of the DSM-IV-TR. There are also minor changes to the other criteria.

Criterion B

Considering that the former formulation of Criterion B1 (*recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions*) carried excessive weight for ruminative, depressive symptoms, and as shown by many studies that due to the non-specific nature of the criterion this led to an overlap of symptoms with other psychiatric disorders, in particular with depression, the DSM-5 decided for the following: *recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)*.

To better reveal intrusive symptoms and dissociated reactions, generally considered as core symptoms for diagnosis, Criteria B2 and B3 were modified. Criterion B2 (distressing nightmares) was better defined such that the content or worries of the nightmare must be correlated with the traumatic event [*recurrent distressing dreams in which the content and/or affect of the dream is related to the event(s)]*. Criterion B3 now specifies that flashbacks are dissociative reactions in which the subject feels or acts as if the traumatic event reoccurs, and that this reaction takes place along a continuum whose extreme expression is represented by a complete loss of awareness of the surrounding environment [b]. Criteria B4 ("intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble some aspect of the traumatic event") and B5 ("marked physiological reaction at ...") were not substantially changed.

Criteria C and D

Criterion C (avoidance and emotional blunting) of the DSM-IV-TR, due to the adoption of a structure with four factors, underwent the most radical changes. In fact, it is now divided into two distinct clusters. The new Criterion C, named *Persistent avoidance of stimuli associated with the traumatic event(s)*, comprises symptoms of persistent avoidance of stimuli associated with the traumatic event. A new symptomatological cluster, new Criterion D, is defined as *Negative alterations in cognitions and mood associated with the traumatic event(s)*, which includes symptoms of emotional blunting of the DSM-IV-TR, emphasizing selected aspects. It also includes two new symptoms, namely *pervasive emotional state* and *persistent negative distorted blame of self or others about the cause or consequences of the traumatic event*.

New Criterion C leaves Criterion C1 (avoidance of distressing memories, thoughts, or feelings about, or closely associated with, the traumatic event) and C2 (avoidance of external stresses, such as people, places, conversations, activities, objects, or situations that evoke distressing memories, thoughts or feelings about the traumatic event, or which are closely related) of the DSM-IV-TR relatively unaltered.

New Criterion D includes 7 items that are derived from previous Criterion C and new criteria. The DSM-5 specifies the primary role of dissociative amnesia in impaired memory and the characteristics of psychic blunting, typical of patients with PTSD, that is extended to include not only the feelings of a shortened future, but also the negative expectations about oneself, others and the world. Thus, the cluster includes: difficulty in remembering important aspects about the traumatic event, seen in terms of dissociative amnesia (D1); persistent beliefs and negative expectations about oneself, others, or the world (D2); unwarranted feelings of blame related to the causes and consequences of the traumatic event (D3); persistent negative emotional state (D4); marked decrease in interest or participation in significant activities (D5); feelings of detachment or estrangement from others (D6); and persistent inability to express positive emotions (D7).

Criterion E

Criterion E is simply the previous Criterion D, relative to "persistent symptoms of increased arousal", to which symptoms of hyperarousal and increased responsiveness, new aspects of risk-taking behaviours, maladaptive and self-destructive or aggressive behaviours have been added [9-12]. The inclusion of aggressive behaviour (Criterion E1) stems from growing evidence, especially in studies of war veterans, that aggressive behaviour, more than other symptoms of PTSD, is often the core of the disorder. Considering self-destructive behaviours (Criterion E2), a marked increase in the propensity to risk-taking behaviour, including for example reckless driving, has

[b] Dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) are recurring (such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.

been shown, especially among adolescents exposed to terroristic acts and probably suffering from PTSD. The following are unchanged: hypervigilance (E3), exaggerated response to threat (E4), problems in concentration (E5) and sleep disturbance (E6).
One likely consequence of the reformulation of this criterion is that there is the possibility to interrelate PTSD to substance abuse and aggression in the family and social context, which are especially frequent In post-traumatic situations [10]. It should be noted that the DSM-5 considers two clinical subtypes of PTSD, *Dissociative Subtype* for patients with persistent or recurrent symptoms of depersonalization and/or derealization and *With Delayed Expression Subtype*, with onset at least 6 months after the event. An important change, lastly, is related to the course of disease, with the elimination of the specifier "acute" vs. "chronic" which currently classifies PTSD depending on its duration, with a cut-off of 3 months.

Conclusions

It should be highlighted that the changes contained in the DSM-5can be summarized in three major points. The first is the removal of PTSD from the section on Anxiety Disorders and the creation of a new section, *Trauma and Stressor Related Disorders*, which contains the following categories in addition to PTSD (*Reactive Attachment Disorder, Disinhibited Social Engagement Disorder, Acute Stress Disorder, Adjustment Disorder, Other Specified Trauma and Stressor Related Disorder*) whose aetiopathogenesis is caused by traumatic stress. This is undoubtedly an interesting change as it places the trauma at the centre of a variety of disorders, highlighting the different possible reactions to psychotraumatic events. The second major change is the attempt to redefine the traumatic event, which in the relatively short existence of PTSD, has undergone a series of changes related to the difficulty in finding the right equilibrium between the need to limit the risk of an excessive number of diagnoses due to the lack of highly specific criteria with diagnostic sensitivity. Lastly, the third key change is the restructuring of symptomatological criteria: the symptomatological structure of PTSD has gone from three to four clusters, with the separation of Avoidance from Numbing, and the revision of several symptoms in order to better identify the disorder. The addition of aggressive (Criterion E1) and self-destructive (Criterion E2) behaviours, which were not foreseen, but which recent studies have shown are clearly correlated with PTSD: aggressive behaviours often manifest in family and social settings, and self-destructive behaviour, which ranges from substance abuse to maladaptive and suicidal gestures. In summary, while the new revisions in the DSM-5 are not a revolution in PTSD, they undoubtedly represent definite forward progress in better definition of the disorder.

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Uso di cannabis ed esordi psicotici: dall'epidemiologia alla clinica

Cannabis use and psychosis onset: from epidemiology to clinical practice

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Summary

Objectives

The aim of this study is to review the most recent literature data regarding association between use of cannabis and psychotic disorders, especially highlighting epidemiological, neurobiological and clinical data.

Methods

A MEDLINE search of the international literature data was performed. The following keywords were used: "cannabis use", "onset psychosis", "high risk of psychosis", "at risk mental state", "epidemiology", "neurobiology" and "clinical features". All studies from the years 2000 to 2011, except for epidemiological studies, were selected. Finally, the most relevant literature was chosen.

Results

Cannabis use is associated with a 2- to 3- fold increase in the relative risk for psychosis in individuals with familial and genetic vulnerability. The results of several prospective studies also show a dose-response relationship between exposure to cannabis and the risk of psychosis after exposure. Many neurobiological studies reported that the Δ^9-tetrahydrocannabinol (Δ^9-THC) is the component of cannabis with the most psychotropic effects that can mediate psychotic onset through alteration of the endocannabinoid signal. A key role in genetic vulnerability to these effects is supported by polymorphisms of the gene for catechol-O-methyl-transferase (i.e., the presence of the gene variant Val/Val compared to Met/Met). More recent studies have shown how the use of cannabis preparations with higher concentrations of Δ^9-THC (e.g., skunk vs. resin vs. leaves) is more associated with onset of psychosis.

Conclusions

According to literature data, we predict an increase in the rates of psychosis over the next 10 years. However, the possibility to eliminate the cannabis use is fairly remote, and clinicians should concentrate their attention on individuals with genetic vulnerability for psychosis and adolescents. In this latter population, increased use and reduction in the age of first consumption has been observed. Therefore, prevention campaigns in schools to reduce the use of cannabis and the risk of psychopathological consequences linked to it are needed. In subjects at risk for psychosis, defined according to the genetic risk (family) for psychosis or the presence of an at-risk mental state, proper psychoeducation on cannabis use is necessary to prevent the onset of overt symptoms and improve long-term outcomes.

Key words

Cannabis • Onset psychosis • At risk mental state • Psychosis

Introduzione

La cannabis è la sostanza illecita più utilizzata al mondo, soprattutto tra gli adolescenti [1 2]. Dagli anni '70, quando la cannabis divenne una sostanza di largo consumo, è, infatti, progressivamente aumentata la percentuale di giovani che ne fa uso e si è assistito a una riduzione dell'età della prima assunzione [3]. Attualmente l'età di inizio dell'abuso di cannabis è nella media-tarda adolescenza, un periodo di importante transizione psicosociale durante il quale gli eventi negativi (ad esempio, lutti, separazioni, fallimenti nelle relazioni interpersonali) hanno un potente impatto sulle scelte di vita [3]. In uno studio di coorte su 2.032 studenti australiani, Patton et al. [4] hanno riportato che il 66% dei maschi e il 52% delle femmine riferivano di utilizzare quotidianamente cannabis e il 75% di essi aveva iniziato l'uso nell'adolescenza. Risultati simili sono stati riportati per altri paesi, quali Nuova Zelanda [5], Regno Unito [6], Stati Uniti [1] e Paesi Bassi [2]. In Italia lo studio IPSAD (*Italian Population Survey on Alcol and Drugs*) del Dipartimento Politiche Antidroga condotto nel primo semestre 2011 su una popolazione di 35.018 studenti (15-19 anni), ha evidenziato che il 22,1% degli studenti aveva provato, almeno una volta nella propria vita, a utilizzare cannabis.

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Il 18,2% del campione aveva riferito un consumo nei 12 mesi precedenti all'indagine, l'11,9% un uso nei precedenti 30 giorni (www.epid.ifc.cnr.it).
Nel 2006, per la prima volta, il rapporto annuale sull'abuso di sostanze delle Nazioni Unite è stato dedicato alle problematiche legate all'uso di cannabis: "È di fondamentale importanza limitare l'uso di cannabis in quanto essa è nella maggior parte del mondo la sostanza illecita più popolare. Si stima che il 4% della popolazione adulta mondiale consumi ogni anno cannabis. In alcuni paesi, più della metà della popolazione giovane riferisce di averla provata" (www.unode.org/unode/en/world_drug_report.html). Il report evidenzia che nei paesi europei, in particolare, c'è stata una crescita smisurata del consumo di cannabis nelle ultime tre decadi del XX secolo, e un aumento nella potenza delle preparazioni di cannabis. Le varietà di cannabis attualmente disponibili sul mercato illecito presentano, infatti, un incremento notevole delle concentrazioni di Δ^9-tetraidrocannabinolo (dal 3-4 al 12-18%) con riduzione di quelle del cannabidiolo (1,5%), con un conseguente aumento della potenza della sostanza dal punto di vista degli effetti psicotropi [7].
L'aumento del consumo di cannabis è stato, inoltre, accompagnato da una riduzione dell'età di inizio nell'uso. Un ampio studio condotto nei Paesi Bassi, infatti, mostra che tra il 1992 e il 1996 il numero di soggetti che hanno iniziato a utilizzare cannabis a 13 anni o prima è raddoppiato [8]. L'uso di cannabis in adolescenza è stato associato a dipendenza dalla sostanza, abuso di altre sostanze illecite [3] e sviluppo di sintomi e disturbi psicotici [9-15]. Recentemente, Henquet et al. [15] hanno osservato che i pazienti con disturbi psicotici sono maggiormente sensibili agli effetti psicotropi della cannabis, soprattutto a causa dei suoi effetti tossici subacuti. Vari studi hanno, inoltre, riportato un'alta prevalenza di uso di sostanze, in particolare cannabis e alcol, tra gli individui al primo episodio di un disturbo psicotico [16-18]. In una revisione della letteratura, Verdoux [19] ha presentato i risultati di diversi studi prospettici riportando una relazione dose-risposta tra l'esposizione alla cannabis e il rischio di psicosi dopo l'esposizione. Molti studi su individui sani hanno, inoltre, evidenziato che la cannabis è un fattore di rischio per lo sviluppo di psicosi in coloro che presentano una vulnerabilità genetica o uno stato mentale a rischio [19].
L'uso di sostanze, in particolare la cannabis, è stato associato a riduzione dell'età all'esordio psicotico [16 20 21], genere maschile [20 21], assenza di deficit cognitivi (ad esempio, fluenza verbale, abilità visuo-spaziali, memoria visiva e verbale, funzioni esecutive, attenzione e processamento precoce delle informazioni) [22-24], ricaduta precoce [25], maggior gravità dei sintomi [17 26-28] e comportamento suicidario [29]. L'aumentato uso di cannabis ha anche un impatto sul decorso a lungo termine, in termini di mancata remissione e aumento di gravità, frequenza e persistenza dei sintomi [10 17 26 30 31].
La valutazione del danno che la cannabis può apportare coinvolge quello che Hall e Pacula [32] hanno descritto come "la scelta degli sfortunati": sebbene la maggior parte dei soggetti che utilizzano cannabis non sperimentano problematiche legate a tale uso, una minoranza degli utilizzatori può sviluppare gravi conseguenze per la salute.
L'obiettivo dello studio è quello di revisionare i più recenti dati di letteratura relativi all'associazione tra uso di cannabis e disturbi psicotici all'esordio con focus sugli aspetti epidemiologici, neurobiologici e clinici. È stata effettuata, pertanto, una revisione accurata della letteratura nazionale e internazionale utilizzando le seguenti parole chiave: *cannabis use* e *onset psychosis*, *high risk of psychosis*, *at risk mental state*, *epidemiology and neurobiology*. Sono stati, quindi selezionati tutti gli studi effettuati dal 2000 al 2011. Per gli studi epidemiologici non sono stati prefissati criteri di selezione in relazione al periodo di pubblicazione. Sono stati, quindi, riportati i dati di letteratura maggiormente significativi per l'argomento trattato.

Evidenze epidemiologiche

L'interesse attuale per il legame tra uso di cannabis e l'associazione con disturbi psicotici, è stato formalizzato in maniera rigorosa in uno studio longitudinale su una popolazione di militari di leva Svedesi [33], che è stato poi replicato ed esteso in una serie di studi longitudinali (Tab. I) [10 11 31 34 35]. Questi studi, inoltre, sono stati ampliati da una serie di studi trasversali su ampie popolazioni [36 37] e su popolazioni ad alto rischio [13 27 38 39]. Tutti gli studi hanno mostrato un aumentato tasso di psicosi o sintomi psicotici nei giovani che utilizzano cannabis. Diversi studi hanno, inoltre, riportato una relazione tra dose di cannabis e rischio di sviluppare un disturbo psicotico con un aumento dell'uso associato a un aumento del rischio di psicosi [10 11 33 35 40 41].
Nello *Studio Longitudinale su una popolazione di militari di leva Svedesi* è stata osservata una relazione dose-risposta tra l'uso di cannabis all'età di 18 anni e la diagnosi di schizofrenia nei 15 anni successivi [33]. I "forti utilizzatori" avevano una probabilità 6 volte maggiore di ricevere una diagnosi di schizofrenia rispetto ai non utilizzatori. Il rischio relativo per lo sviluppo di un disturbo psicotico si riduceva, tuttavia, a 2,3 quando veniva controllata statisticamente la variabile confondente "diagnosi diversa da psicosi", presente in buona parte del campione. Solo il 3% dei "forti utilizzatori" aveva manifestato un disturbo schizofrenico, per cui è stato suggerito che l'uso di cannabis può determinare un aumentato rischio per la schizofrenia solo negli individui che sono vulnerabili. Zammit et al. [40] hanno riportato i dati del follow-up a 27 anni

TABELLA I.
Studi longitudinali relativi a uso di cannabis e sintomi psicotici. *Longitudinal studies relating to cannabis use and psychotic symptoms*.

	Disegno	Sesso	Numero dei partecipanti	Follow-up (anni)	Età degli utilizzatori (anni)	Risultati
Popolazione di militari di leva svedesi [33]	Coorte di militari 1969-1970	Maschi	45.570	15	18	• I "forti utilizzatori" avevano una probabilità 6 volte maggiore di ricevere una diagnosi di schizofrenia rispetto ai non utilizzatori • Il 3% dei "forti utilizzatori" avevano manifestato un disturbo schizofrenico. L'uso di cannabis può determinare un aumentato rischio per la schizofrenia solo negli individui che sono vulnerabili
Popolazione di militari di leva svedesi [40]	Coorte di militari 1969-1970	Maschi	50.053	27	18	• I "forti consumatori" di cannabis avevano un rischio 6,7 volte maggiore, rispetto ai non utilizzatori, di sviluppare un disturbo schizofrenico nei 27 anni successivi • Relazione causale tra l'uso di cannabis e la schizofrenia
NEMESIS (Paesi Bassi) [10]	Studio basato sulla popolazione		4045	3	18-64	• Gli individui che utilizzavano cannabis al baseline presentavano un rischio 3 volte maggiore di sviluppare sintomi psicotici al follow-up • Relazione dose-risposta • Una storia lifetime di uso di cannabis al baseline, rispetto all'uso di cannabis al follow-up, era fortemente predittiva per una psicosi nei 3 anni successivi
Studio Dunedin (Nuova Zelanda) [31]	Coorte di nascita 1972-1973	Maschi e femmine	759	11	15	• I soggetti che avevano utilizzato cannabis all'età di 15 e 18 anni, rispetto a quelli che non l'avevano utilizzata, mostravano percentuali maggiori di sintomi psicotici all'età di 26 anni • Un esordio dell'uso all'età di 15 anni era associato con un'aumentata probabilità di rispettare i criteri per un disturbo schizofreniforme all'età di 26 anni • Significativa esacerbazione o interazione tra l'uso di cannabis all'età di 18 anni e i sintomi psicotici all'età di 11 anni
CHDS (Nuova Zelanda) [42]	Coorte di nascita 1977	Maschi e femmine	1053	21	0-21	• La dipendenza da cannabis è associata a un elevato tasso di sintomi psicotici all'età di 18 e 21 anni
EDSP (Germania) [11]	Coorte di nascita 1970-1981	Maschi e femmine	2437	4	14-24	• L'uso di cannabis nei giovani aumenta il rischio di sviluppare sintomi psicotici • Il rischio di sviluppare sintomi psicotici è maggiore nei soggetti con predisposizione alla psicosi • La predisposizione alla psicosi non è predittivo di utilizzo di cannabis nel follow-up, rigettando l'ipotesi dell'automedicazione
EDSP (Germania) [30]	Coorte di nascita 1970-1981	Maschi e femmine	2210	10	14-24	• L'uso di cannabis aumenta l'incidenza di esperienze psicotiche persistenti • Le esperienze psicotiche non sono predittive di un successivo uso di cannabis

sulla popolazione dello studio precedente [33] con risultati simili. I "forti consumatori" di cannabis all'età di 18 anni, infatti, avevano un rischio 6,7 volte maggiore, rispetto ai non utilizzatori, di sviluppare un disturbo schizofrenico nei 27 anni successivi. Il rischio si riduceva, pur rimanendo sempre significativo, dopo il controllo di fattori confondenti quali i disturbi del comportamento, un basso quoziente intellettivo, il crescere in un ambiente urbano, il fumo di sigaretta e la scarsa integrazione sociale.

Nel *Netherlands Mental Health Interview Survey and Incidence Study* (NEMESIS), uno studio sulla popolazione generale, sono stati valutati, al baseline, dopo 1 anno e dopo 3 anni, 4045 soggetti senza psicosi e 59 con sintomi psicotici autoriferiti [10]. Gli individui che utilizzavano cannabis al baseline, rispetto a quelli che non la utilizzavano, presentavano un rischio 3 volte maggiore di sviluppare sintomi psicotici al follow-up. Tale rischio restava significativo dopo il controllo di una serie di fattori quali l'etnia, lo stato civile, la scolarità e il vivere in ambiente urbano. Gli autori hanno, inoltre, evidenziato una relazione dose-risposta, con un rischio più elevato (*odds ratio* = 6.8) per i soggetti che utilizzavano la sostanza con maggior frequenza. La dose di cannabis assunta è stata valutata in base alla frequenza di utilizzo espressa su una scala 1-5 (quasi tutti i giorni, 3-4 giorni a settimana, 1-2 giorni alla settimana, 1-3 giorni al mese, meno di una volta al mese). Ulteriori analisi, condotte sullo stesso campione, hanno rilevato che una storia lifetime di uso di cannabis al baseline, rispetto all'uso di cannabis al follow-up, era fortemente predittiva di un esordio psicotico nei 3 anni successivi. Questo suggerisce che l'associazione tra uso di cannabis e psicosi non è il mero risultato dell'effetto a breve termine della sostanza. L'uso contemporaneo di altre sostanze, inoltre, non aumentava il rischio di sviluppare una psicosi [10]. Lo studio conferma che "l'uso di cannabis è un fattore di rischio indipendente per l'esordio psicotico e che coloro che sono vulnerabili per un disturbo psicotico sono particolarmente sensibili ai suoi effetti" anche rispetto a un esito peggiore [10].

Il *Dunedin Multidisciplinary Health and Development Study* è uno studio condotto su una coorte di 1037 individui nati a Dunedin nel 1972-1973 (tasso di follow-up del 96% a 26 anni) [31]. Sebbene lo studio sia stato condotto su un numero esiguo di soggetti fornisce informazioni su sintomi psichiatrici auto-riferiti all'età di 11 anni, prima dell'uso di cannabis e permette di esaminare l'inizio dell'uso di cannabis in relazione agli esiti, attraverso la somministrazione di un questionario sull'uso di cannabis alle età di 15 e 18 anni. L'intera coorte è stata, inoltre, valutata dal punto di vista diagnostico all'età di 26 anni con un intervista standardizzata elaborata attraverso i criteri diagnostici del DSM-IV. È stata, quindi, ottenuta una valutazione degli esiti psicotici sia come continuum (attraverso la valutazione dei sintomi) che come disturbo (disturbo schizofreniforme del DSM-IV). I soggetti che avevano utilizzato cannabis all'età di 15 e 18 anni, rispetto a quelli che non l'avevano utilizzata, mostravano percentuali maggiori di sintomi psicotici all'età di 26 anni. L'effetto risultava maggiore per un uso in età più precoce. È stato, infine osservato che il 10,3% dei soggetti che utilizzavano cannabis all'età di 15 anni, rispetto al 3% dei soggetti non utilizzatori, ricevevano una diagnosi di disturbo schizofreniforme all'età di 26 anni. L'uso di cannabis all'età di 15 anni, inoltre, non appariva predittivo di un'evoluzione verso la depressione all'età di 26 anni, mentre l'uso di altre sostanze illecite non era predittivo di un'evoluzione verso la schizofrenia [31]. Tale dato è indicativo di una relazione diretta tra l'uso pregresso di cannabis e la successiva comparsa di una psicosi [31].

Il *Christchurch Health and Development Study* (CHDS) è uno studio longitudinale su una coorte di 1265 soggetti nati nel 1977 a Christchurch in Nuova Zelanda valutati alla nascita, a 4 mesi a 1 anno di età e in seguito annualmente sino al 16° anno, a 18 e 21 anni [42]. Lo studio si propone di valutare il tasso di sintomi psicotici in soggetti con dipendenza da cannabis all'età di 18 e 21 anni. La valutazione all'età di 18 e 21 anni è stata effettuata attraverso la *Simptom Cecklist-90* (SCL-90), per la psicopatologia generale, e per gli item relativi alla dipendenza da cannabis della *Compositive International Diagnostic Interview* (CIDI). I risultati hanno mostrato che i soggetti con dipendenza da cannabis all'età di 18 anni presentavano una percentuale 3.7 volte maggiore di sintomi psicotici rispetto ai non dipendenti, all'età di 21 anni la percentuale è risultata essere 2.3 volte maggiore. Dopo il controllo per fattori confondenti i soggetti con dipendenza da cannabis presentavano una percentuale 1,8 volte maggiore di sintomi psicotici rispetto ai non dipendenti. Gli autori hanno suggerito che i giovani con dipendenza da cannabis dovrebbero essere considerati un gruppo a rischio per sintomi psicotici [42].

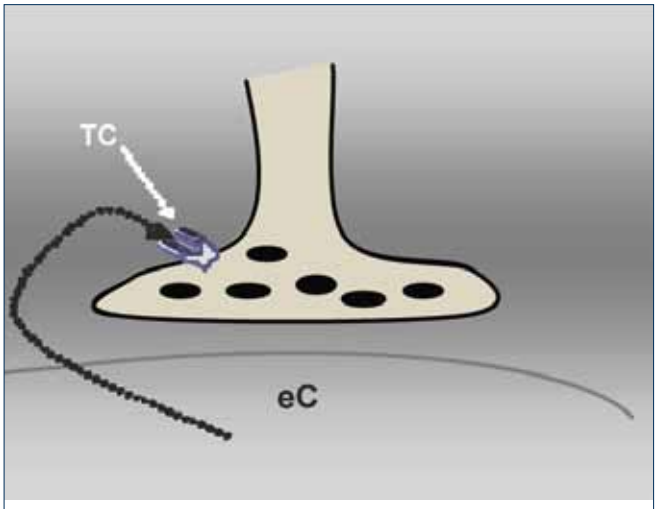
Recentemente, Henquet et al. [11] e Kuepper et al. [30] hanno analizzato i dati, rispettivamente dopo 4 e 10 anni di follow-up, dello studio tedesco *Early Developmental Stage of Psychopathology* (EDSP). L'EDSP è uno studio condotto su una coorte di individui nati a Monaco tra il 1970 e il 1981 con un disegno longitudinale e prospettico che prevede la valutazione, sia della presenza dei sintomi psicotici che l'abuso di cannabis, attraverso una versione rivisitata della *Composite International Diagnostic Interview* (DIA-X-M-CIDI). Henquet et al. [11] hanno valutato i dati dello studio EDSP al baseline e dopo 4 anni di follow-up. In questo studio, per valutare la predisposizione alla psicosi è stata utilizzata, nei due tempi di valutazione, la somma dei punteggi alle sottoscale "ideazione paranoide" e "psicoticismo" della *Symptom Checklist-90*: la predisposizione veniva identificata da un punteggio totale al di sopra del 90° percentile. Gli autori hanno osservato che l'utilizzo di cannabis aumen-

tava il rischio di sintomi psicotici dopo 4 anni con un andamento dose-risposta. L'effetto dell'utilizzo di cannabis sull'esito psicotico era maggiore nei soggetti che presentavano una predisposizione alla psicosi al baseline. La frazione del rischio attribuibile alla popolazione (FAP) era 6,2% nell'intero campione e 14,2% nel gruppo con predisposizione alla psicosi. Una predisposizione alla psicosi, tuttavia, non era predittiva di uso di cannabis nel follow-up. Nello studio di Kuepper et al. [30] sono stati utilizzati i dati dell'EDSP su 2.210 soggetti valutati nei tempi baseline, T2 (follow-up a 4 anni) e T3 (follow-up a 10 anni). L'incidenza di sintomi psicotici nei soggetti esposti a cannabis era 31% (*vs.* 20% nei non esposti) al T2 e 14% al T3 (*vs.* 8% nei non esposti). L'utilizzo lifetime di cannabis al T2 aumentava il rischio di esperienze psicotiche al T3. La presenza di esperienze psicotiche al T2, invece, non era predittiva di un utilizzo di cannabis al T3. Tale dato sembra, quindi, non confermare l'ipotesi che l'impiego di cannabis successivo all'esordio di un disturbo psicotico potesse rappresentare un tentativo di automedicazione. È stata, inoltre, osservata un'associazione significativa tra prosecuzione dell'uso di cannabis e rischio di persistenza di esperienze psicotiche [30].

Tutti gli studi epidemiologici riportati suggeriscono che l'uso di cannabis rappresenta un fattore di rischio ambientale che impatta sul rischio di psicosi attraverso l'aumento del rischio di incidenza di esperienze psicotiche e, per un uso continuato nel tempo, attraverso il rischio di manifestare sintomi psicotici persistenti che possono determinare una transizione verso un disturbo [30]. Diversi studi, inoltre, hanno osservato una relazione dose-risposta tra esposizione alla cannabis e il successivo sviluppo di un disturbo psicotico [10 11 33 40]. In tutti gli studi, tuttavia, la "dose" di cannabis assunta non è stata stabilita attraverso il dosaggio urinario della sostanza ma valutando la frequenza di utilizzo. Andreasson et al. [33] e Zammit et al. [40], ad esempio, definiscono "forti consumatori" i soggetti che hanno utilizzato cannabis per più di 50 volte. Van Os et al. [10], invece, hanno utilizzato la frequenza cumulativa dell'esposizione longitudinale alla cannabis attraverso la valutazione dell'uso nei tre tempi (baseline, T1 e T2) con una scala autosomministrata a 5 punti (1: quasi tutti i giorni; 2: 3-4 giorni a settimana; 3: 1-2 giorni a settimana; 4: 1-3 giorni al mese; 5: meno di 1 volta al mese). Henquet et al. [11] hanno, infine, valutato la dose attraverso la frequenza di utilizzo: non uso; meno di 1 volta al mese; 3-4 volte al mese; 1-2 volte al mese; 3-4 volte a settimana; giornalmente. Gli studi futuri, pertanto, dovrebbero definire in maniera più accurata la dose di cannabis assunta anche attraverso il dosaggio dei cannabinoidi urinari in modo da chiarire il rapporto dose-risposta tra assunzione di tale sostanza e il rischio di psicosi.

Evidenze neurobiologiche

Gli effetti psicotropi della cannabis sono dovuti in gran parte dagli effetti del Δ^9-tetraidrocannabinolo (Δ^9-THC) sui recettori cerebrali specifici per i cannabinoidi [43]. Sono stati identificati tre tipi di recettori per i cannabinoidi: CB1, CB2 e CB3. Il recettore CB1 è quello più rappresentato e ha un'alta densità nelle regioni cerebrali che regolano il comportamento emotivo e cognitivo, quali corteccia prefrontale e cingolata, amigdala, ippocampo, striato e gangli della base [44 45]. Su tali recettori agiscono i cannabinoidi endogeni o endocannabinoidi, tra cui l'anandamide e il 2-arachidonilglicerolo. Gli endocannabinoidi segnalano in direzione retrograda, dai dendriti ai terminali assonali (Fig. 1). I recettori CB1 regolano, inibendo l'apertura dei canali del calcio voltaggio dipendenti, il rilascio di vari neurotrasmettitori chiave, tra cui acido amino-γ-butirrico (GABA), glutammato, dopamina, noradrenalina, serotonina e acetilcolina [45 46]. Pertanto, l'uso di cannabis può determinare una cascata di cambiamenti nel funzionamento neurotrasmettitoriale. Gli effetti precisi di questi cambiamenti chimici sulla funzione cerebrale sono difficili da definire in quanto dipendono dal tempo della diffusione del Δ^9-THC e dal tipo di recettori per i cannabinoidi attivato [43 46]. Gli effetti psicologici della cannabis, tuttavia, sembrano essere il risultato di un'alterazione, del segnale normalmente trasmesso dal recettore CB1 [44] (Fig. 1).



Gli endocannabinoidi sono sintetizzati nei neuroni post-sinaptici e diffusi ai terminali pre-sinapstici dove stimolano i recettori CB1. Anche la cannabis (Δ^9-tetraidrocannabinolo: TCH) attiva i recettori CB1. L'alterazione del segnale endocannabinoide fisiologico sembra determinare gli effetti fisiologici del THC.

FIGURA 1.
Endocannabinoidi come modulatori sinaptici. *Endocannabinoidi as synaptic modulators.*

Nonostante la complessità degli effetti del Δ^9-THC sul cervello, le evidenze derivate da studi animali e umani suggeriscono che esso ha effetti a breve termine sulle funzioni comportamentali e cognitive [47]. Negli animali questi effetti includono un potenziamento del comportamento stereotipato causato dalle amfetamine, che molti ritengono essere legato al comportamento psicotico negli umani [47]. Negli umani, la somministrazione di alte dosi di Δ^9-THC induce alterazioni endofenotipiche simili a quelle osservate nei soggetti schizofrenici, quali la riduzione della componente P300 dei potenziali evocati [48] o la riduzione dell'inibizione dello "startle reflex" [48 49]. In uno studio sugli effetti acuti del Δ^9-THC in pazienti con un disturbo schizofrenico in fase di stabilizzazione, D'Souza et al. [50] hanno osservato una esacerbazione dei sintomi, sia positivi che negativi, e dei deficit cognitivi. Queste risposte non sono permanenti e sembrano riflettere gli effetti transitori del Δ^9-THC sul funzionamento comportamentale e cognitivo [51]. Tuttavia, un esposizione ripetuta al Δ^9-THC in soggetti vulnerabili può determinare modificazioni permanenti nel funzionamento neurotrasmettitoriale che a lungo termine potrebbe portare allo sviluppo di disturbi psicotici [51]. Leweke et al. [52] hanno, inoltre, riportato che l'esposizione frequente (uso lifetime maggiore di 20 volte) alla cannabis può determinare una sottoregolazione del segnale dell'*anandamide* nei soggetti con un primo episodio schizofrenico ma non nei controlli sani. Gli autori suggeriscono che l'alterazione del segnale di questo endocannabinoide potrebbe essere una componente importante attraverso la quale la cannabis agisce sul funzionamento del SNC determinando i suoi effetti nocivi, tra cui lo sviluppo di esperienze psicotiche [52].

Le vie neurobiologiche che legano l'uso di cannabis all'insorgenza di sintomi psicotici non sono completamente chiare. Verosimilmente queste vie coinvolgono gli effetti del Δ^9-THC sulla regolazione di dopamina e serotonina [53]. È stato dimostrato che, in base alla regione cerebrale interessata, la stimolazione dei recettori per i cannabinoidi da parte del Δ^9-THC può sia inibire che aumentare il rilascio di dopamina [54 55]. Cheer et al. [55] hanno riportato che le sostanze che attivano i recettori CB1 aumentano il rilascio di dopamina nel sistema limbico. Voruganti et al. [56] hanno, infine, rilevato che un soggetto con schizofrenia, a due immagini SPECT (tomografia a emissione di singolo fotone) consecutive, mostrava, dopo l'uso di cannabis, una riduzione del 20% del legame dei recettori dopaminergici striatali, suggestiva di un aumento dell'attività dopaminergica nelle sinapsi.

L'opinione che gli effetti dopaminergici sono una via attraverso la quale la cannabis può determinare psicosi è supportata dalla ricerca genetica-comportamentale. Caspi et al. [34], infatti, hanno dimostrato che i polimorfismi genetici dell'enzima catecol-o-metiltransferasi (COMT), implicato nella regolazione del metabolismo della dopamina, modulano l'effetto psicogenetico dell'uso di cannabis nell'adolescenza. Gli autori hanno osservato che i soggetti utilizzatori di cannabis con la variante Val/Val del gene per la COMT presentavano un rischio di sviluppare un disturbo schizofreniforme aumentato di 5 volte circa. Un assetto allelico Met/Met dello stesso gene offre una protezione relativa (odds ratio 1,1), mentre gli eterozigoti (Val/Met) hanno un rischio intermedio (odds ratio 2,5). Non sembrano, inoltre, esserci correlazioni tra il genotipo della COMT e l'uso di cannabis, ovvero il genotipo della COMT non influenza il consumo di cannabis [34]. Questi dati rappresentano il primo esempio di come un'interazione tra assetto genetico e fattori ambientali predispone allo sviluppo di psicosi. I risultati riportati da Caspi et al. [34] corroborano l'ipotesi per cui l'effetto della cannabis sul rilascio di dopamina può essere uno dei meccanismi attraverso i quali la sostanza può determinare sintomi psicotici e un aumentato rischio per i disturbi psicotici. Recentemente, studi effettuati con la tomografia a emissione di positroni (PET) e studi post-mortem hanno mostrato che la variante allelica Val/Val del gene per la COMT è associata a un marcato aumento della sintesi di dopamina nei neuroni mesencefalici che proiettano allo striato ventrale [57]. Inoltre, Ludica e Riegel [58] hanno riportato che la cannabis aumenta la scarica neuronale dopaminergica e che gli agonisti dei recettori CB1, come il Δ^9-THC, aumentano il rilascio di dopamina nei terminali dello striato e della corteccia prefrontale. Questi dati potrebbero spiegare perché i soggetti con la variante Val/Val per la COMT sono più vulnerabili agli effetti psicogenici dei cannabinoidi esogeni.

L'uso di cannabis compromette la memoria esplicita, ovvero la memoria per le informazioni codificate coscientemente, che è mediata da un'aumentata scarica delle sinapsi eccitatorie (glutammaergiche) dell'ippocampo [59 60]. Recentemente, sono stati evidenziati recettori CB1 nelle terminazioni nervose eccitatorie dell'ippocampo [61 62]. Studi animali, inoltre, hanno mostrato che l'uso di cannabis determina un blocco del potenziale a lungo termine delle sinapsi eccitatorie compromettendo l'apprendimento mediato dalle regioni ippocampali. Robbe et al. [63], inoltre, hanno riportato che la somministrazione sistemica di un agonista sintetico del CB1 determina una riduzione dell'attività dei neuroni ippocampali. Al contrario, gli antagonisti del recettore CB1 o la delezione del gene che codifica per esso abbassano la soglia per l'induzione del potenziale a lungo termine delle sinapsi eccitatorie dell'ippocampo e, quindi, migliorano l'apprendimento e la memoria [44].

Gli studi sopra riportati suggeriscono che una variante allelica Val/Val per la COMT, il consumo frequente di cannabis e un suo utilizzo in età precoce, aumentano il rischio per futuri disturbi psichiatrici. Recentemente è

stato dimostrato, infatti, che un inizio dell'uso durante l'adolescenza aumenta la vulnerabilità verso disturbi psicotici [64].

In un recente studio, Morgan et al. [65] hanno osservato che il cannabidiolo (CBD) (un ulteriore composto della cannabis) antagonizza gli effetti del Δ^9-THC. Il CBD potrebbe, infatti, proteggere contro gli effetti cognitivi del Δ^9-THC. In questo studio naturalistico, i partecipanti venivano invitati a scegliere e consumare una delle formulazioni di cannabis a disposizione che differivano in base al contenuto di CBD. Sono stati, quindi, valutati attraverso una serie di compiti e questionari cognitivi. Gli individui che selezionavano una formulazione con alti livelli di CBD non mostravano deficit cognitivi nell'area della memoria dopo il consumo di cannabis rispetto a quelli che consumavano una formulazione con bassi livelli di CBD, che presentavano un significativo peggioramento delle funzioni mnesiche. Precedentemente, gli stessi autori hanno dimostrato che gli individui che consumavano cannabis a basso contenuto di CBD e più elevato contenuto di Δ^9-THC riportavano maggiori esperienze psicotiche rispetto a coloro che fumavano cannabis con elevati livelli di CBD [66]. Il CBD sembra avere una bassa affinità per il recettore CB1 e potrebbe esercitare i suoi effetti inibendo la ricaptazione dell'anandamide [67]. Nel tentativo di capire i meccanismi biologici alla base dell'interazione tra Δ^9-THC e CBD, Bhattacharyya et al. [68] hanno osservato effetti opposti di Δ^9-THC e CBD sull'attività cerebrale utilizzando la risonanza magnetica funzionale. Hanno, infatti, riportato che il Δ^9-THC attenuava l'attività dello striato e contemporaneamente induceva sintomi psicotici, mentre il CBD determinava un aumento dell'attività dello striato. Recentemente, lo stesso gruppo di ricerca [69] ha dimostrato che, durante l'esecuzione di compiti che attivano la salienza attenzionale, il Δ^9-THC e il CBD modulano in maniera differente la funzione prefrontale, striatale e ippocampale. La somministrazione di Δ^9-THC prima dell'esecuzione dei compiti determinava un'attivazione attenuata del caudato e aumentata della regione prefrontale destra. La somministrazione di Δ^9-THC determinava, inoltre, una riduzione nella latenza delle risposte in funzione del suo effetto sull'attivazione del caudato destro. Gli effetti della CBD sulle performance nei compiti di attivazione della salienza attenzionale, avevano una direzione opposta agli effetti del Δ^9-THC, con un aumentata attivazione del caudato e dell'ippocampo e un'attivazione attenuata nella regione prefrontale destra. Secondo gli autori questa differente attivazione può contribuire agli effetti della cannabis sui sintomi psicotici e sul rischio di sviluppare disturbi psicotici [69].

I dati riportati sottolineano l'importanza di tener conto delle differenze nella potenza delle preparazioni di cannabis. La potenza della cannabis varia ampiamente tra i diversi prodotti: la resina di cannabis sembra contenere livelli simili di Δ^9-THC e CBD, mentre le foglie di cannabis contengono moderate concentrazioni di THC e scarse di CBD; la sinsemilla, o skunk, contiene alti livelli di Δ^9-THC mentre il CBD è assente [70]. Le prime evidenze che formulazioni diverse di cannabis possono avere un impatto differenziale sui rischi per la salute mentale sono state fornite da Di Forti et al. [71], i quali hanno riportato che gli individui con un primo episodio di psicosi avevano consumato una formulazione a più alta potenza (ovvero lo skunk) per un più lungo periodo di tempo e con maggiore frequenza rispetto ai controlli sani. Pertanto, l'utilizzo di "skunk" che contiene elevate concentrazioni di Δ^9-THC e basse concentrazioni di CBD è stato associato con un rischio maggiore di problemi di salute mentale. Gli studi neurobiologici esaminati riportano come il Δ^9-THC sia il componente della cannabis con maggiori effetti psicotropi che possono mediare l'insorgenza di un disturbo psicotico attraverso l'alterazione del segnale cannabinoide endogeno. Un ruolo fondamentale nella vulnerabilità genetica a tali effetti è sostenuto dal polimorfismo del gene che codifica per la COMT ovvero dalla presenza della variante genica Val/Val per tale gene rispetto a quella Met/Met [34]. I vari studi mostrano, infine, che l'utilizzo di cannabis potrebbe determinare un'alterazione del segnale dopaminergico che giustificherebbe gli effetti comportamentali, cognitivi e sulla senso percezione della sostanza. Tale alterazione potrebbe, infine, mediare la transizione verso un esordio psicotico negli utilizzatori di cannabis.

Studi di morfologia cerebrale

Gli studi mormometrici relativi a uso di cannabis ed esordio di disturbi psicotici sono di numero esiguo [72-74]. Questa tipologia di studi potrebbe essere utile nel definire il legame tra cannabis e psicosi attraverso l'analisi delle alterazioni cerebrali presenti negli utilizzatori di cannabis con predisposizione verso un disturbo psicotico (Tab. II). Szeszko et al. [72] hanno osservato in soggetti al primo episodio psicotico che utilizzavano cannabis alterazioni nella sostanza grigia del cingolato anteriore, ma non del giro frontale superiore e orbito frontale. Rais et al. [73] hanno, inoltre, riportato che nei pazienti al primo episodio che avevano utilizzato cannabis, rispetto ai non utilizzatori, era presente una riduzione rilevante del volume cerebrale globale durante 5 anni di follow-up [73]. Bangalore et al. [74] hanno effettuato un analisi morfometrica per valutare le alterazioni della sostanza grigia nei pazienti al primo episodio psicotico che utilizzavano cannabis rispetto a quelli che non la utilizzavano e ai controlli sani, riportando nei primi una riduzione della sostanza grigia nella corteccia del cingolato posteriore di destra. Recentemente, Stone et al. [75] hanno riportato che, sia in soggetti sani che con stato mentale a rischio (SMR), l'uso

TABELLA II.
Studi morfometrici sugli individui utilizzatori di cannabis all'esordio psicotico. *Morphometric studies on cannabis users at onset psychosis*.

Autori	Disegno	Risultati
Szsesko et al. [72]	• 51 soggetti al primo episodio psicotico (20 utilizzatori di cannabis e 31 non utilizzatori) • 56 volontari sani • RMN	• Deficit nella sostanza grigia del *cingolato anteriore*, ma non del giro frontale superiore e orbito frontale, nei soggetti al primo episodio psicotico che utilizzavano cannabis
Bangalore et al. [74]	• 30 soggetti al primo episodio schizofrenico (15 utilizzatori di cannabis e 24 non utilizzatori) • 42 volontari sani • RMN	• Riduzione della sostanza grigia nella corteccia del *cingolato posteriore di destra*, una regione ricca di recettori CB1, nei soggetti all'esordio che utilizzavano cannabis
Rais et al. [73]	• 51 soggetti con esordio schizofrenico recente (19 utilizzatori di cannabis e 32 non utilizzatori) • 31 volontari sani • RMN • Follow-up 5 anni	• Riduzione più pronunciata del *volume cerebrale* durante 5 anni di follow-up nei pazienti al primo episodio che avevano utilizzato cannabis rispetto ai non utilizzatori
Stone et al. [75]	• 27 soggetti con SMR • 27 volontari sani • RMN	• L'uso di cannabis inversamente correlato al volume della sostanza grigia della corteccia prefrontale • Non erano presenti evidenze a supporto dell'ipotesi di un'aumentata suscettibilità agli effetti dannosi di alcol e cannabis sulla sostanza grigia regionale in soggetti con uno SMR • Un uso moderato di alcol, tabacco e cannabis era associato a una ridotta sostanza grigia nelle varie regioni esaminate sia i soggetti con uno SMR che in volontari sani

RMN: Risonanza Magnetica; SMR: stato mentale a rischio.

di cannabis era inversamente correlato al volume della sostanza grigia della corteccia prefrontale. Non erano presenti evidenze a supporto dell'ipotesi di un'aumentata suscettibilità agli effetti dannosi di alcol e cannabis sulla sostanza grigia prefrontale in soggetti con uno SMR. Tuttavia, un uso moderato di alcol, tabacco e cannabis era associato a una riduzione della sostanza grigia nelle varie regioni esaminate sia i soggetti con uno SMR che in volontari sani. Tale dato potrebbe essere rappresentativo di un danno corticale o di cambiamenti della plasticità neuronale in coloro che utilizzano cannabis, tabacco e alcol.

Ruolo causale della cannabis nei disturbi psicotici

Negli ultimi quindici anni sono stati effettuati diversi studi per definire il legame tra l'uso di cannabis e lo sviluppo di psicosi o di sintomi psicotici con risultati convergenti che suggeriscono che l'uso di cannabis può essere un fattore di rischio indipendente per l'esordio psicotico [10 31 76-78].

La natura del legame tra cannabis e psicosi, tuttavia, non è stato ancora ben spiegato. I risultati ottenuti dai campioni clinici di soggetti con psicosi hanno un valore limitato per spiegare i meccanismi sottostanti a tale associazione, in quanto sono difficilmente controllabili i potenziali fattori confondenti legati al quadro clinico (ad esempio, sintomatologia attiva e deficit cognitivi legati alla condizione patologica). Pertanto, gli studi che esplorano le variabili implicate nell'espressione di sintomi psicotici in popolazioni non cliniche, rispetto a quelli condotti su popolazioni cliniche, possono essere di maggior aiuto nell'identificare i fattori di rischio per lo sviluppo di un disturbo psicotico [79 80]. Tali studi sono stati condotti su soggetti con propensione alla psicosi, ovvero in coloro che presentano esperienze psicotiche ma non hanno una diagnosi clinica di psicosi. Sono, quindi, inclusi i cosiddetti segni schizotipici e i sintomi psicotici attenuati che sono presenti in una relativamente ampia proporzione (15-20%) di coloro che non hanno una diagnosi clinica di psicosi [79 81].

I primi studi si sono focalizzati sull'associazione tra cannabis e propensione psicotica "positiva". Williams et al. [82] hanno riportato un punteggio maggiore a una scala che

esplorava i sintomi schizotipici "positivi" (alterazioni della percezione, pensiero magico o paranoide) in soggetti reclutati dalla popolazione generale, che utilizzavano cannabis rispetto a quelli che non la consumavano. Kwapil et al. [83] hanno effettuato uno studio longitudinale con un follow-up a 10 anni su 534 studenti universitari valutati al baseline sulle dimensioni schizotipiche "positive" e "negative". I risultati dello studio hanno mostrato che i soggetti con un maggior punteggio nella dimensione positiva al baseline presentavano una più alta frequenza di uso di sostanze nei 10 anni successivi.

Studi più recenti si sono focalizzati sul legame tra cannabis e le diverse dimensioni della propensione alla psicosi. Skosnik et al. [84] hanno riportato differenze significative alle varie dimensioni dello *Schizotypal Personality Questionnaire* (SPQ) tra i soggetti con uso attuale e quelli con uso pregresso di cannabis e coloro che non ne hanno mai fatto uso, riscontrando nei primi punteggi maggiori alle dimensioni "positive" e alla sottoscala "comportamento bizzarro". Non sono state riportate associazioni, invece, tra uso di cannabis e punteggi delle dimensioni negative. Nunn et al. [85] hanno valutato 196 studenti con l'*Oxford-Liverpool Inventory of Feeling and Experiences* (O-LIFE *psychosis proneness*) e con la *Peter et al. Delusional Inventory* (PDI), dividendoli in quattro gruppi: utilizzatori di cannabis, utilizzatori di alcol, utilizzatori di cannabis e alcol e non utilizzatori. I soggetti che utilizzavano solo cannabis, rispetto ai soggetti degli altri gruppi, hanno mostrato punteggi più elevati alle scale che valutano i sintomi positivi (esperienze insolite dell'O-LIFE e della PDI). Solo due studi hanno mostrato un legame tra uso di cannabis e sintomi "negativi" [86 87]. Dumas et al. [86] hanno riportato in giovani studenti che utilizzavano cannabis, rispetto a quelli che non la utilizzavano, punteggi maggiori ai sintomi positivi e alle dimensioni negative dell'SPQ. Verdoux et al. [87] hanno evidenziato, in giovani studentesse, un'associazione significativa tra l'uso di cannabis e alti punteggi alle dimensioni "positive" e "negative" del *Community Assessment of Psychic Experiences* (CAPE), un questionario per la valutazione delle esperienze psicotiche nella popolazione generale. Non era, invece, presente un'associazione tra l'uso di cannabis e la dimensione "depressiva" del CAPE.

Si può, quindi, concludere che gli studi che hanno esplorato l'associazione tra uso di cannabis e propensione alla psicosi in popolazioni non cliniche hanno fornito risultati che dimostrano una relazione tra la presenza di caratteristiche della dimensione "positiva" della propensione alla psicosi (ad esempio, distorsioni percettive e ideative, comportamenti bizzarri) e l'uso di cannabis. Sono stati, tuttavia, rilevati risultati discrepanti sulla relazione tra uso di cannabis e le dimensioni "negative" della propensione alla psicosi (ad esempio, ritiro sociale, affettività ristretta, anedonia). Tale discordanza potrebbe riflettere il fatto che i segni negativi sono difficilmente valutabili con una scala autosomministrata. Il maggiore ostacolo nella valutazione della dimensione negativa nei campioni clinici e non clinici è legato alla capacità degli strumenti di discriminare tra sintomi negativi e depressivi. Tuttavia, una "sindrome amotivazionale", caratterizzata da perdita di interessi e di motivazione e compromissione del funzionamento lavorativo, è stata osservata nei "forti" consumatori di cannabis ed è probabilmente indotta da un'encefalopatia subacuta legata all'intossicazione cronica [88]. Questa sindrome presenta similitudini fenomenologiche con la dimensione "negativa" della psicosi e la relazione dose-risposta tra la frequenza dell'uso di cannabis e l'intensità dei sintomi negativi osservata nello studio di Verdoux et al. [87] potrebbe confermare indirettamente l'esistenza di tale fenomeno. È stato, inoltre, suggerito che i soggetti con psicosi userebbero la cannabis come automedicazione per i sintomi negativi [84]. I soggetti con psicosi che utilizzano cannabis, inoltre, presentano più frequentemente sintomi positivi, rispetto a quelli negativi, un miglior funzionamento premorboso e una minor gravità del disturbo [89]. Quindi, la bassa frequenza dell'uso di cannabis nei soggetti con una prominente sintomatologia negativa potrebbe essere conseguenza dei sintomi negativi e dello scarso funzionamento premorboso. È, infatti, richiesto un certo livello di competenze sociali per ottenere le sostanze illecite e i soggetti con una sintomatologia negativa hanno un accesso limitato alle sostanze a causa della compromissione di questa area del funzionamento.

Il maggior limite degli studi trasversali, in popolazioni non cliniche, che mostrano come l'utilizzo di cannabis sia associato a esperienze psicotiche, è rappresentato dal fatto che non definiscono definitivamente la direzione della causalità.

Esistono tre potenziali vie causali che possono spiegare il legame uso di cannabis e psicosi:

1. la cannabis potrebbe agire attraverso cambiamenti neurochimici, aumentando la vulnerabilità ai sintomi psicotici;
2. i soggetti che sviluppano psicosi potrebbero avere un'aumentata vulnerabilità all'uso di cannabis come conseguenza del loro stato psicologico e probabilmente come un tentativo di automedicazione;
3. l'uso di cannabis e la psicosi potrebbero essere reciprocamente correlate attraverso un nodo di feedback nel quale l'uso di cannabis aumenta il rischio di psicosi e allo stesso tempo l'esordio di un disturbo psicotico potrebbe determinare un aumentato consumo di cannabis.

Per risolvere il problema della direzione della causalità tra utilizzo di cannabis e psicosi, è necessario indagare l'effetto della cannabis sul manifestarsi di esperienze psicotiche in maniera prospettica in popolazioni non

cliniche. Una revisione sistematica di studi clinici randomizzati che confrontano gli effetti antiemetici della cannabis con placebo e altri antiemetici mostra che il 6% dei pazienti che aveva assunto cannabis presentava allucinazioni e il 5% "paranoia", mentre nessun paziente trattato con gli altri farmaci di controllo aveva presentato tali "effetti collaterali" [90].

Per caratterizzare meglio la relazione temporale tra uso di cannabis e sintomi psicotici, sono stati condotti quattro studi principali.

Verdoux et al. [87] hanno indagato l'impatto dell'uso di cannabis sull'esordio di esperienze psicotiche utilizzando l'*Experience Sampling Method* (ESM), una tecnica strutturata di diario, dove giovani soggetti, con "basso" o "alto" utilizzo di cannabis, dovevano riportare variabili ambientali, attività e sensazioni per 5 volte al giorno in 7 giorni consecutivi. L'analisi dei risultati ha suggerito che l'uso di cannabis deve essere considerato un fattore di rischio per l'insorgenza acuta e temporanea di alterazioni della percezione.

Fergusson et al. [35] in uno studio longitudinale a 25 anni su 1265 bambini neozelandesi, hanno utilizzato due modelli di equazione strutturale per valutare l'effetto causale tra l'uso di cannabis e i sintomi psicotici. Gli autori hanno rilevato una relazione causale tra uso di cannabis e sviluppo di sintomi psicotici. La presenza di sintomi psicotici, invece, non incideva sulla scelta di utilizzare cannabis. Hanno, inoltre, ipotizzato che l'aumento dei sintomi psicotici può inibire l'uso di cannabis.

Recentemente, Cougnard et al. [91] hanno valutato l'interazione tra i fattori ambientali (quali l'uso di cannabis, i traumi infantili, il vivere in ambiente urbano) e la presenza di esperienze psicotiche al *baseline* nel predire sintomi psicotici dopo 3 anni di follow-up, riportando che i fattori di rischio ambientali per la psicosi agiscono in maniera additiva e sinergica nella persistenza di esperienze psicotiche.

McGrath et al. [41] hanno valutato, in 3801 giovani adulti nati tra il 1981 e il 1984 tra cui 228 coppie di fratelli, l'uso di cannabis e 3 tipi di esiti psicotici (psicosi affettiva, allucinazioni, e punteggio alla *Peters Delusions Inventory* a un follow-up di 21 anni). L'uso precoce di cannabis è stato associato a un esordio psicotico precoce. Gli studi su coppie di fratelli permettono di ridurre la probabilità che i risultati possano essere spiegati da altri fattori confondenti. Questo studio fornisce un ulteriore sostegno all'ipotesi per cui l'uso precoce di cannabis è un fattore di rischio modificabile per lo sviluppo di psicosi nell'età giovane adulta.

Dai risultati di uno studio di coorte sulla popolazione generale con un follow-up di 10 anni, infine, emerge che l'uso di cannabis rappresenta un fattore di rischio ambientale che aumenta l'incidenza di esperienze psicotiche e, se l'uso è continuo nel tempo, aumenta il rischio di esperienze psicotiche persistenti che potrebbero determinare l'esordio di un disturbo psicotico [30]. La persistenza delle esperienze psicotiche, determinata dall'uso di cannabis, viene considerata come un indicatore della predisposizione per un disturbo psicotico attraverso un processo di sensibilizzazione, per cui l'esposizione ripetuta a uno stressor (uso di cannabis) porta progressivamente a risposte di maggiore entità ovvero a sintomi psicotici di gravità tale da portare all'insorgenza di un disturbo psicotico franco [30].

L'ipotesi dell'automedicazione non è supportata dagli studi epidemiologici [10 11 30] per cui l'uso di cannabis è un fattore di rischio per l'insorgenza di sintomi psicotici, mentre la presenza di sintomi psicotici non predispone all'utilizzo di tale sostanza. Questi risultati sono rafforzati dallo studio di Verdoux et al. [87] in cui gli utilizzatori di cannabis riferiscono di aver sperimentato "percezioni insolite" in seguito all'uso della sostanza piuttosto che aver utilizzato cannabis per cercare di fronteggiare la presenza di "percezioni insolite". A favore dell'ipotesi dell'automedicazione troviamo un solo studio [41]. McGrath et al. [41] riportano, infatti, che gli individui con allucinazioni autoriferite all'età di 14 anni presentavano un più frequente uso di cannabis all'età di 21 anni.

Uso di cannabis ed esordio dello spettro psicotico

La maggior parte delle evidenze epidemiologiche mostra che l'uso di cannabis è molto frequente tra i soggetti che presentano un disturbo psicotico. Tre delle maggiori indagini epidemiologiche internazionali hanno, infatti, evidenziato una maggior frequenza di uso di sostanze, in particolare la cannabis, nei soggetti con disturbo schizofrenico rispetto alla popolazione generale [76 92 93].

Il *National Epidemiological Catchment Area* (ECA), il più importante studio epidemiologico sulle patologie psichiatriche degli Stati Uniti condotto sulla popolazione generale, riporta che i soggetti che presentavano almeno un sintomo psicotico mostravano un tasso più alto di uso giornaliero di cannabis (10,1%) rispetto a coloro che non avevano riferito alcun sintomo psicotico (4,8%) [92]. Gli autori riferiscono che i soggetti che utilizzavano giornalmente cannabis erano 2,4 volte a rischio per esperienze psicotiche.

Il *National Psychiatric Morbidity Survey* (NPMS) mostra che il 5% dei pazienti con schizofrenia o disturbo delirante riferiva di aver utilizzato cannabis nell'anno precedente l'intervista [93].

Il *National Survey of Mental Health and Well-Being* australiano mostra che il 12% dei soggetti con diagnosi di schizofrenia rispettava anche i criteri per l'ICD-10 per disturbo da uso di cannabinoidi. Gli individui con diagnosi ICD-10 di disturbo da dipendenza di cannabis avevano,

inoltre, una probabilità 3 volte maggiore di ricevere una diagnosi di schizofrenia rispetto a quelli senza disturbo da dipendenza da cannabis [76].

L'alcol e la cannabis sembrano essere le principali sostanze utilizzate dai pazienti all'esordio. Sono stati effettuati vari studi retrospettivi per valutare l'uso di sostanze in pazienti all'esordio di un disturbo psicotico. Tali studi, tuttavia, presentano dei *recall bias* in quanto sono basati su indagini retrospettive.

Sevy et al. [22] hanno riportato che il 23% di un campione di 118 pazienti con un primo episodio di schizofrenia o di disturbo schizoaffettivo rispettava i criteri per un disturbo da uso di sostanze. Tra i pazienti con un disturbo da uso di sostanze, l'età di inizio dell'uso di sostanze precede l'età di esordio del disturbo psicotico di molti anni e solo in una minoranza di casi i due esordi coincidono [22].

Hambrecht e Hafner [94] hanno riportato che il 13% di 232 pazienti con esordio schizofrenico aveva una storia di abuso di cannabis.

Addington e Addington [18] hanno esaminato la prevalenza dell'uso di sostanze e il suo impatto sull'esito dopo tre anni dal primo episodio psicotico. Gli autori hanno riportato che il 52% dei soggetti valutati mostra una comorbidità con un disturbo da uso di sostanze e che nel 32% dei casi la sostanza era la cannabis e nel 35% l'alcol. Come in altri studi l'uso di cocaina, altri stimolanti, oppioidi e sedativi era raro. L'uso di cannabis e alcol nei tre anni era correlato in maniera significativa a sesso maschile, età più giovane ed esordio precoce. Non c'erano differenze tra gli utilizzatori di tali sostanze e i non utilizzatori nelle valutazioni sul funzionamento sociale e sui sintomi, anche se coloro che utilizzavano cannabis presentavano una maggior gravità dei sintomi positivi in tutti i tempi di valutazione e della depressione a 1 anno dall'esordio.

Risultati simili sono stati osservati da uno studio italiano condotto su soggetti al primo episodio di schizofrenia ricoverati presso L'Ospedale Maggiore di Milano. I risultati mostrano che il 34,7% dei soggetti ha avuto una storia di abuso di sostanze e la cannabis è risultata la sostanza più frequentemente utilizzata (49%), seguita dall'alcol (13%) e dalla cocaina (4%). Gli abusatori mostravano un più alto punteggio agli item della *Brief Psychiatric Rating Scale* (BPRS) "disturbo del pensiero" e "ostilità" [95]. Recentemente, il nostro gruppo ha valutato l'influenza dell'uso di cannabis sul quadro psicopatologico, sulla sua gravità e sul funzionamento globale di 67 soggetti reclutati presso il Servizio di Monitoraggio e Intervento precoce per la Lotta agli Esordi della sofferenza mentale e psicologica nei giovani (SMILE) di L'Aquila con diagnosi (DSM-IV) di esordio dello spettro bipolare (n = 49), esordio dello spettro schizofrenico (n = 5) e di stato mentale a rischio (n = 13) secondo i criteri della CAARMS (*Comprensive Assessment of the At Risk. Mental State*) [96]. Il campione totale è stato suddiviso in due gruppi: il primo formato da 30 soggetti con uso di cannabinoidi nel mese precedente la valutazione e il secondo di 37 soggetti che non avevano mai utilizzato la sostanza. I soggetti che avevano utilizzato cannabis nel mese precedente la valutazione presentano punteggi medi significativamente più elevati alle dimensioni della SCL-90 "Aggressività" e "Psicoticismo" e una maggiore gravità del disturbo valutato attraverso la *Clinical Global Impression-Severity* (CGI-S). Non erano presenti differenze tra gli utilizzatori di cannabis e i non utilizzatori nelle valutazioni sul funzionamento globale. La dimensione "psicoticismo" della SCL-90 e un punteggio maggiore alla CGI-S, inoltre, discriminavano il gruppo degli utilizzatori di cannabis. I risultati dello studio suggeriscono che, in soggetti con esordio di un disturbo psicotico o con SMR, la valutazione dell'uso di cannabis potrebbe aggiungere informazioni cliniche alla descrizione psicopatologica e diagnostica, distinguendo un sottogruppo di soggetti all'esordio [96].

La maggior parte degli studi, tuttavia, non è in grado di stabilire se le manifestazioni prodromiche della schizofrenia precedono l'uso di cannabis, lasciando la possibilità che l'uso di cannabis può rappresentare la conseguenza di una schizofrenia sommersa piuttosto che la causa della stessa. Vari studi, infatti, indicano che la schizofrenia è tipicamente preceduta da modificazioni psicologiche e comportamentali che si manifestano anni prima della diagnosi. Lo *Studio di Dunedin* è l'unico a dimostrare l'ordine di precedenza temporale evidenziando che gli adolescenti utilizzatori di cannabis sono ad aumentato rischio di sperimentare sintomi psicotici nell'età adulta, persino dopo aver preso in considerazione i sintomi psicotici infantili che precedono l'uso di cannabis [31].

I vari studi che indagano l'impatto della cannabis negli esordi psicotici suggeriscono che l'uso di cannabis non è chiaramente una causa necessaria per lo sviluppo della schizofrenia, in quanto non tutti gli adulti con un disturbo psicotico hanno utilizzato cannabis durante l'adolescenza. È anche chiaro che tale uso non è una causa sufficiente per lo sviluppo successivo di psicosi, in quanto la maggior parte degli adolescenti che utilizzano cannabis non sviluppano un disturbo psicotico da adulti.

Uso di cannabis e stato mentale a rischio

Il campo dello "stato mentale a rischio" (SMR) è uno dei più recenti sviluppi in Psichiatria. Il termine è stato coniato da McGorry e Singh [97] per meglio definire lo stato prodromico della psicosi. Esso deriva dal greco *prodromos* che significa precursore di un evento. In medicina, "prodromo" si riferisce a sintomi e segni precoci di una malattia che precedono le manifestazioni caratteristiche della forma acuta e completamente sviluppata. La fase prodromica dei disturbi dello spettro psicotico corrisponde al periodo in cui inizia il processo patologico ma non sono

presenti sintomi psicotici prominenti ed è rappresentata da una deviazione del comportamento e dell'esperienza precedente [98]. Come nella clinica medica, il prodromo è un concetto retrospettivo, diagnosticato solo dopo lo sviluppo dei sintomi e dei segni definitivi. Il prodromo, tuttavia, deve essere considerato come un processo, non come una lista di sintomi, in cui i cambiamenti nell'esperienza e nel comportamento si instaurano nel tempo.
Sono stati effettuati cinque studi relativi all'uso di cannabis nei soggetti con SMR [27 99-102] (Tab. III).
L'*Edinburgh High Risk Study* ha valutato 155 individui, tra i 16 e i 25 anni, con rischio genetico per schizofrenia per la presenza di almeno 2 familiari di primo o secondo grado affetti da schizofrenia ma senza sintomatologia in atto e 36 controlli senza familiarità reclutati nella popolazione generale. I risultati evidenziano che sia gli individui con alto rischio genetico per schizofrenia che gli individui senza storia familiare di schizofrenia avevano un aumentato rischio di sviluppare sintomi psicotici dopo il consumo di cannabinoidi [27].
Phillips et al. [99] hanno condotto uno studio prospettico su 100 individui che afferivano a un servizio di intervento precoce, riportando che l'uso o la dipendenza da cannabis non era associata allo sviluppo di disturbo psicotico (transizione alla psicosi) in un periodo di follow-up di 12 mesi dopo l'entrata nello studio. Tuttavia, il basso livello di uso di cannabis riportato in quest'ultimo studio potrebbe indicare che il campione non è rappresentativo della popolazione di individui con prodromi.
Kristensen e Cadenhead [100] hanno valutato 48 soggetti afferenti al *Cognitive Assessment and Risk Evaluation* (CARE) *Program*, programma longitudinale per gli individui identificati a rischio per schizofrenia sulla base della presenza di sintomi psicotici subsindromici e/o storia familiare di psicosi. A 1 anno di follow-up solo il 12,5% dei soggetti ha avuto una transizione a psicosi e l'83,3% di essi rispettava

TABELLA III.
Uso di cannabis e sintomi prodromici. *Cannabis use and prodromal symptoms*.

Autori	Disegno	Numero dei partecipanti	Risultati
Miller et al. [27]	*Edinburgh High Risk Study* • Individui ad alto rischio di 16-25 anni con almeno 2 familiari di primo o secondo grado affetti da schizofrenia	155	• Sia gli individui con alto rischio genetico per schizofrenia (in virtù di due familiari affetti) che gli individui senza storia familiare di schizofrenia avevano un aumentato rischio di sviluppare sintomi psicotici dopo il consumo di cannabinoidi
Phillips et al. [99]	Studio prospettico • Coorte di soggetti ad alto rischio per psicosi • Follow-up 12 mesi	100	• L'uso o la dipendenza da cannabis non era associata allo sviluppo di disturbo psicotico (transizione alla psicosi) in un periodo di follow-up di 12 mesi dopo l'entrata nello studio
Kristensen e Cadenhead [100]	Studio prospettico • soggetti (12-30 anni) afferenti al *Cognitive Assessment and Risk Evaluation* (CARE) *Program* • Follow-up 2 anni	48	• Significativa associazione tra abuso di cannabis e conversione verso la psicosi nei soggetti ad alto rischio
Corcoran et al. [101]	Studio prospettico • Soggetti (12-25 anni) con prodromi psicotici afferenti al *Center of Prevention and Evaluation* (COPE) *research program* • Follow-up 12 mesi	32	• I soggetti che utilizzavano cannabis, rispetto ai non utilizzatori, presentavano maggiori disturbi percettivi e un peggioramento del funzionamento nei periodi in cui incrementavano l'uso della sostanza • Nei soggetti ad alto rischio per psicosi l'uso di cannabis potrebbe rappresentare un fattore di rischio per l'esacerbazione dei sintomi psicotici sottosoglia, soprattutto i disturbi della percezione
Miettunen et al. [102]	Studio basato sulla popolazione • Adolescenti (15-16 anni) popolazione generale Finlandese	6330	• I soggetti che utilizzavano cannabis presentavano 3 o più sintomi prodromici • Relazione tra frequenza dell'uso di cannabis e aumento dei sintomi prodromici

i criteri per abuso o dipendenza di cannabis. Gli autori hanno riportato una significativa associazione tra abuso di cannabis e conversione verso la psicosi.
Recentemente, Corcoran et al. [101] hanno effettuato uno studio prospettico attraverso la valutazione longitudinale (follow-up a 2 anni) di 32 soggetti con sintomi prodromici, di cui 13 utilizzavano cannabis, afferenti al *Center of Prevention and Evaluation* (COPE) *research program*. I soggetti che utilizzavano cannabis, rispetto ai non utilizzatori, presentavano maggiori disturbi percettivi e un peggioramento del funzionamento nei periodi in cui incrementavano l'uso della sostanza. Gli autori hanno suggerito che nei soggetti con propensione allo sviluppo di un disturbo psicotico l'uso di cannabis potrebbe rappresentare un fattore di rischio per l'esacerbazione dei sintomi psicotici sottosoglia, soprattutto di disturbi della percezione.
Miettunen et al. [102] hanno condotto uno studio su una popolazione di 6.330 adolescenti finlandesi (15-16 anni) valutando la presenza di sintomi prodromici e l'uso di cannabis. I soggetti che utilizzavano cannabis presentavano 3 o più sintomi prodromici. Viene, inoltre, riportata una relazione tra frequenza dell'uso di cannabis e aumento dei sintomi prodromici.
Gli studi riportati [27 100-102], tranne quello di Phillips et al. [99], evidenziano come l'uso di cannabis può influenzare l'espressione di sintomi prodromici e la conversione in psicosi nei soggetti con un alto rischio per lo sviluppo del disturbo in virtù della presenza di sintomi psicotici sottosoglia, di una predisposizione genetica o di un recente deterioramento del funzionamento globale. Pertanto, risulta di primaria importanza l'applicazione di un programma psicoeducazionale sul rischio di conversione a psicosi nei soggetti con uno SMR che utilizzano cannabis al fine di prevenire l'esordio del disturbo.

Conclusioni

L'uso di cannabis è considerato un fattore di rischio, tra molti altri (ad esempio, traumi infantili, vivere in ambiente urbano) che formano una costellazione di cause che può favorire l'esordio di un disturbo psicotico [12]. Dall'analisi degli studi riportati si rileva, infatti, che l'uso di cannabis può aumentare il rischio per lo sviluppo di un disturbo psicotico soprattutto nei soggetti vulnerabili [10 31]. Verdoux [19], inoltre, ha riportato che tra gli utilizzatori di cannabis, effetti avversi di tipo psicologico erano più comuni in coloro che avevano una "propensione alla psicosi".
L'uso di cannabis determina un aumento di 2 o 3 volte del rischio relativo per un disturbo psicotico. Bisogna, tuttavia, valutare la Frazione Attribuibile alla Popolazione (FAP), ovvero la misura dei numeri di casi del disturbo nella popolazione generale che potrebbe essere evitato attraverso la rimozione di un fattore causale dannoso. Il FAP per lo studio di Dunedin è 8, ovvero rimuovendo l'uso di cannabis dalla popolazione Neozelandese di 15 anni si avrebbe una riduzione dell'8% nell'incidenza della schizofrenia in quella popolazione [31]. Lo studio NEMESIS riporta un FAP più alto, verosimilmente dovuto alla valutazione degli esiti che non includeva solo i casi clinici di psicosi, ovvero in trattamento per un disturbo psicotico [10]. In base ai dati riportati si potrebbe predire un aumento nei tassi di schizofrenia nei prossimi 10 anni. Tuttavia, la possibilità di eliminare totalmente l'uso di cannabis è piuttosto remota ed è consigliabile concentrarsi soprattutto su coloro in cui gli esiti avversi di tale uso sono più comuni [12] e sulla popolazione adolescenziale in cui è stato osservato negli ultimi anni un aumento dell'uso con rischio di dipendenza dalla sostanza, abuso di altre sostanze illecite [3], sviluppo di sintomi e disturbi psicotici [9-15]. Risultano, pertanto, di fondamentale importanza campagne di prevenzione nelle scuole al fine di ridurre l'uso di cannabis e, quindi, il rischio di conseguenze psicopatologiche legate a esso nella popolazione giovanile il cui sistema nervoso centrale è in una fase di modellamento per cui risulta particolarmente sensibile alle sostanze che agiscono sul fisiologico neurotrofismo. Nei soggetti a rischio di un esordio psicotico, definibili in base al rischio genetico (familiarità) o alla presenza di uno SMR, una corretta psicoeducazione all'uso di cannabis è di fondamentale importanza per di prevenire l'insorgenza di una sintomatologia franca e di migliorare gli esiti a lungo termine nel disturbo [103].
Nel 2007 il giornalista Jonathan Owen ha pubblicato un articolo su "The Independent" con titolo *Cannabis: An apology* comunicando che il giornale ha invertito la sua campagna per la depenalizzazione dell'uso di cannabis. Nell'articolo sono riportati dati epidemiologici che dimostrano come la cannabis "causa malattia mentale e psicosi" (http://www.independent.co.uk/life-style/health-and-families/health-news/cannabis-an-apology-440730.html). Il cambiamento di posizione di "The Independent", dopo dieci anni di campagna per la depenalizzazione della sostanza, dimostra come i risultati degli studi effettuati nell'ultimo decennio per valutare il legame tra cannabis e psicosi abbiano influenzato anche l'opinione dei non professionisti. Le attuali conoscenze sull'effetto della cannabis ovvero dei suoi principi attivi (THC e CBD) e delle varie formulazioni sul sistema nervoso centrale e sul ruolo nell'insorgenza di disturbi psicotici dovrebbe portare a campagne di prevenzione più accurate e mirate soprattutto alla fascia di età adolescenziale. Le varie formulazioni (foglie, resina, skunk) e i vari principi attivi (i.e., THC che promuove l'esordio psicotico e CBD con verosimile effetto antipsicotico) della sostanza sono, infatti, concausa di disturbi psicotici soprattutto nei soggetti giovani geneticamente vulnerabili.

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Psychopatological severity index and dissociative symptomatology in a group of non-psychotic outpatients

Indici di gravità psicopatologica e sintomatologia dissociativa in una popolazione di pazienti ambulatoriali non psicotici

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Summary

Dissociative symptoms are a set of symptoms frequently encountered in clinical practice, but they are often underestimated by many clinicians, who in the routine assessment of the patient underrate or not diagnose, emphasizing instead the importance of more classic and obvious symptoms, such as those related to the sphere of mood, anxiety or psychosis. In this way, dissociative symptoms often lose their descriptive complexity, although purely psychopathological, of the very complex clinical status that often underlie dissociative symptoms and dissociative dynamics. For these reasons, this study assessed psychopathological dimensions of mood and anxiety disorders in a transnosographic way. The purpose of the study is to demonstrate that dissociative symptoms, although placed in the diagnostic category of dissociative disorders, have a common thread that correlates with the main manifestations detected in routine clinical practice, and that they may be susceptible to intervention by the physician, even in a nonspecific way on the main symptom, not dissociative, that is treated.

Key words

Dissociative disorders • Dissociation • Anxiety • Depression • Bipolar disorder • Obsessive-compulsive disorder • Stress

The diagnosis of dissociative disorders, as a group of categorical independent nosographic entities, was first included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-III in 1980; before that, dissociative symptomatology was included among psychopathological phenomena ascribed to hysteria [1]. The essential characteristic of dissociative disorders, according to the DSM-IV-TR, is the disconnection of functions (physiologically integrated), of consciousness, memory and perception of identity [2]. The term dissociative was introduced by James in 1890 as a translation of the French term *désagrégation* coined by Pierre Janet in 1889; with this term, the French author individuated the failure of mental integration of 'experiences' (perceptions, memories, thoughts, emotions) that are normally concatenated with each other in the flow of consciousness[1]. Dissociation leads to fragmentation of the unitary sense of self in patients who experience it, cancelling the unity of chronological, biographical and perceptual identity, which every individual normally has [3]. In studies on hysteria (1893-1895), Freud elaborated a psychodynamic theory of dissociation (opposed to the psychopathological one of Janet, linked to passive ego deficits) based on active removal, in affected subjects, of traumatic material within a psychodynamic conflict. In both models, dissociation appears to be closely related to the presence of a traumatic event [1]. Recent studies have shown that the post-traumatic aetiological aspect of dissociative episodes identifies a part of dissociative symptomatology (about 50%), but not the entire dissociative spectrum [4]. The dissociative spectrum (Fig. 1) is composed of a large continuum of dissociative symptomatology along a gradient of severity [1].

Such a spectrum even includes, according to some authors, somatoform disorders and can be divided into three groups:

- *non-clinical or subclinical dissociative experiences*, such as being so deeply assorbed in the contemplation of a movie or immersed in one's own thoughts,that there is no awareness or realization of the surrounding environment (absorption);
- *transient dissociative phenomena in response to external events (trauma, induced states of trance);*
- *clinically-relevant dissociative phenomena*, either in association with other psychiatric disturbances (e.g.

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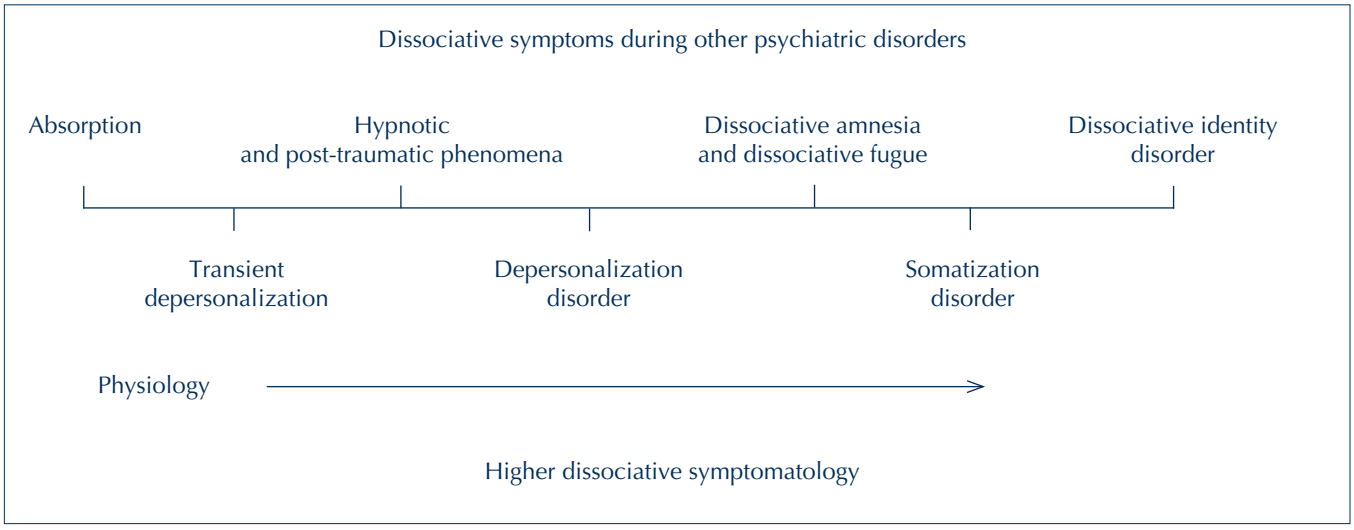

FIGURE 1.
Continuum of dissociative symptomatology and related dissociative disorders. *Continuum della sintomatologia dissociativa e relativi disturbi dissociativi.*

PTSD), or as a defined nosographic category (depersonalization disorder, dissociative amnesia, dissociative fugue, dissociative identity disorder and dissociative disorder not otherwise specified).

According to some authors, the prevalence of dissociative disorders in clinical practice is underestimated, which may be in part due to the lack of inclusion of diagnostic criteria for dissociative disorders in the algorithm of the Structured Clinical Interview for the diagnosis of Axis I disorders in the DSM-IV (SCID-I), as well as the lack of large population-based studies [3]; at present, the prevalence of dissociative disorders in the general population is estimated to be from 5.6% to 10% [1].
At the same time, there is some evidence regarding the association of dissociative symptoms with some psychopathological dimensions, (in particular with obsessions [5], depression and anxiety [6], psychotic symptoms [7 8] and with the severity of a psychiatric disorders [5]). Moreover, it has been observed that patients affected with dissociative disorders have levels of psychopathology (assessed with SCL90-R) that are significantly greater than those in psychiatric patients who are non-dissociators[10]. Considering this, the aim of the present study was to investigate the relation between dissociative symptomatology, psychopathological dimensions (assessed with SCL90-R) and clinical severity in an out-patient population.

Materials and methods

Over an 18-month period, a total of 83 patients (of 213 contacted) were recruited among those presenting to the out-patient psychopharmacological clinic at Policlinico Umberto I, during the first visit. Inclusion criteria included: diagnosis of anxiety, mood and somatoform disorder and adaptation; score > 17 on at least one of the Hamilton scales (A or D). Exclusion criteria were: psychotic disorder, illiteracy, unable to understand questionnaires, presence of a neurodegenerative disease, concomitant diagnosis of epilepsy or on-going problem with addiction.
The study protocol included the administration of a questionnaire for personal data, authorization to keep sensitive data, evaluation scales completed by a clinician (*Clinical Global Impression* [CGI], *Hamilton Anxiety Rating Scale* [HAM-A], *Hamilton Depression Rating Scale* [HAM-D]); self-evaluation questionnaires relative to general psychiatric symptoms (*Symptom Checklist-90-Revised-SCL90-R*) and dissociative symptomatology (*Dissociative Experiences Scale* [DES]).
The CGI evaluates general clinical severity of the patient using a scale from 0 to 7 (0 = Not assessed 1 = Normal, not at all ill, 2 = Borderline mentally ill, 3 = Mildly ill, 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, 7 = Among the most extremely ill patients); the two Hamilton scales evaluate anxiety symptoms (score ≥18 considered pathological) and depression (score ≥ 25 = severe depression; 18-24 = moderate depression; 8-17 = slight depression; ≤ 7 absence of depression).
The SCL 90-R assesses 9 psychopathological dimensions (*somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, psychoticism*), and on the basis of the total score considering 90 *items*, the *Global Severity Index* (GSI) can be calculated; a value greater than 0.566 is con-

sidered indicative of clinically-relevant psychopathology. Using the DES, dissociative symptomatology was evaluated dimensionally and transnosographically. The DES is a self-rating scale that measures the level and type of dissociative experience present (the period of evaluation is lifelong, in general) without considering the diagnosis; it is quick to compile and is composed of 30 questions that consider a score from 0 to 100 in intervals of 10; overall mean global scores higher than 20 are indicative for the presence of a dissociative disturbance [9]. Through a diagnostic interview, for each patient, a diagnosis was formulated based on the criteria in the DSM IV-TR [2].

The SPSS 13 programme was used for statistical analysis, and the distribution of variance was analyzed using the Kolmogorov-Smirnov test. Based on the results of the quantitative distribution of variables (e.g. CGI and age did not have a normal distribution), non-parametric statistical analyses were carried out. Correlations between quantitative variables were evaluated with Spearman's rho test. A $p < 0.05$ was considered statistically significant.

Results

The sample population was recruited over a period of 18 months. A total of 83 patients were included, with a mean age of 46.75 (± 15.33) years (*range* 17-82); there were 51 females and 32 males. The presence of disorders according to DSM-IV TR criteria, are shown in Table 1. Mood and anxiety disorders were present in similar proportions (42.17% and 38.55%, respectively).

From a descriptive analysis of the psychometric parameters evaluated (Table II), the sample cohort had intermediate levels of dissociation from normal (DES <20), intermediate levels of clinically-significant anxiety and depression (HAM-D and HAM-A >17) and moderate global clinical levels of disease (mean CGI = 4); the level of psychopathology as revealed by the self-administered SCL90-R (GSI) test was clinically significant (GSI > 0.566).

The psychopathological dimension of the SCL90-R most frequently seen was depression, obsessive-compulsive, anxiety, somatization, paranoid ideation and interpersonal sensitivity. The indices of psychopathological severity from the GSI and CGI were significantly correlated with the severity of dissociative symptomology (DES). Each psychopathological dimension investigated using the SCL90-R test showed a significant correlation with the dissociative symptomology score ($p < 0.001$). The Hamilton scales did not show any significant correlation with the severity of dissociation.

TABLE I.
Stratification of the sample according to diagnostic area. *Stratificazione del campione in funzione delle aree diagnostiche DSM IV-TR.*

Diagnostic area	N	%
Anxiety disorders	32	38.55
Mood disorders (monopolar)	18	21.69
Mood disorders (bipolar)	17	20.48
Adaptive disorders	11	13.25
Somatoform disorders	5	6.03

Conclusions

The aim of the present study was to investigate correlations between severity of psychopathological manifestations and dissociative symptomology. Our results showed that the intensity of dissociative symptoms appeared to be directly proportional to the severity of the psychopathological dimensions considering both the GSI and CGI. In addition, the severity of dissociation seems to be correlated with severity of each psychopathological dimension assessed with the SCL90-R. Previous studies have shown a relationship between some psychopathological dimensions and dissociative symptomology in patients grouped by the type of disorder [5-8]. It has also been demonstrated that in patients with dissociative disorders the psychopathological dimension of the SCL90-R was significantly higher compared to psychiatric patients that were not affected by dissociative disorders [10]. The data from our patient cohort allowed for the individuation, in a transnosographic manner, of a close relation between psychopathological severity and the level of dissociation. From a clinical standpoint, in our opinion, these results should prompt considerations regarding the relevance of dissociative symptomology during a psychiatric visit as a tool for future integrated and personalized approaches to treatment. Considering psychological disturbances in a hodological context, or as the manifestations of functional disconnection between different brain areas, as suggested by Ffytche [11], the results of our study are suggestive of the possibility that the dissociative symptomology represents a quantitative manifestation of alterations in cerebral circuits; at the same time, the psychopathological dimensions would qualitatively identify areas that are disconnected. Such a hodological vision of psychopathology, lastly, brings us back to the definition of dissociative disorders as a manifestation of *désagrégation* of brain function originally described by Janet. Further studies on larger patient series, using neuroimaging techniques, instruments to assess neurophysiopathological function and mental tests, are needed to evaluate the reliability of our results and their interpretation.

TABLE II.
Descriptive statistics and correlations. *Statistica descrittiva e correlazioni.*

Descriptive Statistics			Statistical correlation	
Parameter	Mean	SD	Correlation coefficient Spearman's rho test	Sig (2 code)
DES	13.800	14.900	1.000	–
Ham-A	18.870	4.420	- 0.075	0.533
Ham-D	16.980	4.670	0.117	0.326
CGI	4.000	0.563	0.233	0.049
GSI	1.286	0.687	0.757	0.000
Somatization	1.302	0.787	0.497	0.000
Obsessive/compulsivity	1.575	0.949	0.677	0.000
Interpersonal sensitivity	1.172	0.871	0.716	0.000
Depression	1.703	0.878	0.603	0.000
Anxiety	1.514	0.809	0.540	0.000
Anger/hostility	0.873	0.802	0.655	0.000
Phobic anxiety	0.775	0.920	0.396	0.000
Paranoid ideation	1.196	0.964	0.616	0.000
Psychoticism	0.892	0.761	0.725	0.000

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Depictions of community care for the mentally ill in two English newspapers: a pilot, qualitative study

Descrizione dell'assistenza territoriale per le persone affette da malattia mentale in due quotidiani inglesi: uno studio qualitativo pilota

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Summary

Objectives

Depictions of mental illness in print media are predominantly negative, and concentrate disproportionately on bizarre behaviours. The present study explores depictions of community care for the mentally ill in print media in the UK.

Methods

By sampling two English newspapers, we retrospectively collected relevant items that were assessed by content and thematic analyses.

Results

The overwhelming proportion of items were related to negative, violent representations. More than half of all items depicted the care of the mentally ill within the community as dangerous. The thematic analysis identified four themes: risk of dangerousness and threat; vulnerability; human rights; mental illness/psychiatric patient. Three of these produced a stigmatizing depiction of the mentally ill.

Conclusions

Inappropriate language was the main concern as along with particular framing devices, they may contribute to the social stigma associated with mental illness.

Key words

Qualitative evaluation • Printed Media • Mentally ill persons • Community mental health services

Introduction

The public's primary sources of information about mental illness are based on a range of media [1 2]. Depictions of mental illness in print media are predominantly negative [3 4], and consistently link mental disorders with violence, failure and unpredictability [5-7]. Furthermore, following the policy of deinstitutionalization of people with serious mental illness, the negative themes of disorder, crisis and risk were found to increasingly predominate in the reporting of mental health issues [8]. Media portrayals of people living with mental illness in the community rely on 'experts' and other third parties who speak generically, and often unsympathetically, about mental disorders [9]. However, depictions of mental illnesses and related community care are relatively common in the print media and often biased towards the more severe forms of mental illness, concentrating disproportionately on bizarre behaviours [5].

Aims and research questions

The present study was undertaken with a view to exploring depictions of community care for the mentally ill in print media in the UK. The following research question was addressed: How do the print media portray community care for the mentally ill in the UK?

We set out to retrospectively collect a sample of newspapers that had depicted community care for the mentally ill. We deliberately chose a relatively remote time period as media coverage during financial crises is known to be biased [10]. Primary goals were: (a) to search for any positive representations of community care for the mentally ill; (b) to search for neutral representations of community care for the mentally ill; (c) to search for negative representations of community care for the mentally ill; and (d) to analyze how community care for the mentally ill was depicted or represented within each item.

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Methods

Rationale

Qualitative research methods, i.e. combined content and thematic analyses [11], are particularly suited for exploring media documents as a key to eliciting how newspaper articles depict community care for the mentally ill.

Sampling

A purposive sampling strategy was used, focusing on two English Newspapers with widely recognized but different audiences, namely the Guardian and the Daily Mail.
The Guardian website (www.guardian.co.uk) and the Daily Mail website (www.dailymail.co.uk) were searched using the search phrase "community care" AND "mentally ill" on July 31st, 2005. Terms associated with mental illness (e.g. 'mad', 'madness', 'insane') were also included. The Guardian website archive yielded 132 items between January 6th, 1999 and July 14th, 2005, published on The Guardian (76), Guardian Unlimited (44) and The Observer (12). The Daily Mail website archive yielded 123 items between March 28th, 2001 and May 19th, 2005. The corpus of collected materials ran to 255 items ranging from brief 'fillers' to full-page newspaper articles. Each item was critically read, and items that were not relevant were discarded, resulting in 48 items.
Each included item was firstly classified according to three variables. These were: (a) positive, (b) neutral and (c) negative representations of community care for the mentally ill. This assessment was subjectively but independently performed by the authors according to: a) the way items framed stories (whether the headline and the content directed the reader to what is in the frame and to ignore what is excluded); b) the use of inappropriate language and/or of psychiatric and medical terminology out of context; c) the presence of dramatic or sensationalist tone or the use of hype; d) the use of celebrity, to offer a role model (destigmatizing and positioning in a positive light, community care for the mentally ill). Inter-coder reliability was 87%.
Furthermore, particular themes, whether positive or negative, were identified and classified following recent findings in Australia [11]. The particular emphasis in this work was to identify the patterns or themes (clusters of mutually consistent discursive resources; words, images and storylines) in the depiction of community care for the mentally ill. Furthermore, the thematic analysis reliability was preserved using two investigators to seek consensus through exhaustive discussion in interpretation. In reporting our analyses, each theme is outlined, followed by a description of its use in the news stories.

Results

Forty-eight items were included that depicted community care for the mentally ill and published in two newspapers: 37 from the Guardian archive and 11 from the Daily Mail archive. These most commonly consisted of news articles or editorial pieces (n = 42, 87.5%).

Content analysis

The depictions of community care for the mentally ill were predominantly negative 28 (58%), while positive and neutral depictions were both 10 (21% and 21%). The negative depictions from the Guardian Archive were 24 of 37, and 9 of 11 from the Daily Mail; the neutral were 8 of 37 for the Guardian and 2 of 11 for the Daily Mail; finally, the positive depictions were 5 of 37 for the Guardian and 1 of 11 for the Daily Mail.

Thematic analysis

Four themes were identified: a) risk of dangerousness and threat; b) human rights; c) vulnerability; d) mental illness/psychiatric patient.

Risk of dangerousness and threat

Within the items, dangerousness was represented by the notion of "a serious and imminent threat to public safety". The concept occurred many times for a number of different cases.

Why was a dangerous schizophrenic free to kill?

A probe is to be launched into how a paranoid schizophrenic with a long history of mental illness was free to stab to death a brave police officer. (The Daily Mail, 19/05/05 – News section)

For instance, this news story included a one-paragraph report of the attack, and a long paragraph about responsibility and threat related to his/her treatment in the community:
Prosecutor […] questioned the wisdom of treating […] in the community
with robust and open criticism against the Trust involved:
The defendant's brother, who declined to give his first name, said he felt […] should not have been released into the community […]. He said: "He has been let down by the system and that's it. […] "He has been ill for more than 10 years. There's nobody done nothing for him. He should have been in care at the time."
A similar theme was found in an earlier case:

Samaritan's killing reveals flaws in care

Deficiencies in community services for the mentally ill were exposed yesterday by an independent inquiry into the killing of a Good Samaritan by the disturbed teenager she befriended (The Guardian, 19/09/2000) complemented by a description of supposed NHS failures:
Lack of appropriate contingency plans for his aftercare "fell short of good clinical practice" and the service's lack of resources made it "impotent to go in and assess his mental state in a time of emergency".

which can also become a frank blame against mental health services.

Accident blackspots

Many tragedies involving mentally ill people can be predicted and even prevented, but mental health services are not paying sufficient attention to the warning signs (The Guardian, 19/07/2004) and their practices:
As in many other cases, had his parents been listened to and his history known, the doctors would not have made an initially incorrect diagnosis, provided inadequate treatment and underestimated the risk that he posed.
The theme is replicated in a similar report, adding a sensationalist tone:

Care and killing in the community

… set out on an insane mission to kill when he walked unhindered out of a supposedly secure psychiatric clinic at […] Hospital (The Daily Mail, 23/03/05)
Despite previous homicidal assaults and a deteriorating mental state, he wasn't properly looked after.
With an explicit criticism for community care for mental health and amalgamating different conditions into the same statement:
the fact remains that there are more than 40 killings a year by patients who shouldn't be on the streets - to say nothing of the hundreds of suicides by the mentally ill who would be better off in hospital.
Furthermore, the tone of sensationalism can be found also in a further item:

Man jailed for life for killing stranger

A schizophrenic who killed a stranger after being released from a secure mental hospital was sentenced to life imprisonment today (The Daily Mail, 30/10/03 – News section).
And the matching of the violent behaviour and schizophrenia:
the schizophrenic […] stabbed retired accountant […] more than 30 times in the head and neck, leaving him unrecognisable to his widow […].

Vulnerability

Personal helplessness and an inability to control or cope with one's life seem components of this theme. In some items, patients, by definition, are subject to the actions of others and this sense of vulnerability and passivity dominates the depiction of the (psychiatric) patient more vulnerable than the typical patient.

Rough treatment of the mentally ill

… was asked to leave [.] hospital shortly before her father helped her kill herself (The Guardian, 15/05/2001).
Or more generally

Forgotten generation' of mental illness sufferers

The needs of 50,000 people with severe mental illness in the UK are still being ignored, campaigners have warned (The Daily Mail, 25/04/05 – Health section)
Emphasizing impairments and needs in daily life
… they want to be remembered, to be seen and heard […] they want to take greater control over their lives.

Human rights

The only potentially positive theme, human rights, was partly limited by being fragmented in the source material. However, the human rights discourse assumes the existence of rights to which any person is entitled. Claiming these rights on behalf of an individual constitutes an implicit claim that the individual is an ordinary person.
Generic civil rights like discrimination are claimed as in the following item:

When illness is ignored

People with mental health problems face discrimination from financial providers and retailers, and have no protection under the law. (The Guardian, 25/06/2005).
It is further pointed out that:
People experiencing the manic phase of manic depression, for example, commonly spend large amounts of money on goods and services which they do not need and cannot afford.
And complaining that:
Neither retailers nor banks are obliged to take into account one's mental state at the time when financial transactions are made. The Banking Code only promises that: "We will consider cases of financial difficulty sympathetically and positively."
The right of a proper employment is also claimed:

Service users call for real job opportunities

Most mental health service users want to hold down demanding jobs but are only offered confidence-boosting training that ill equips them to return to a competitive job market (The Guardian, 14/02/2001.
Emphasizing the partnership with mental health staff:
Pioneering mental health professionals want the NHS to end this by promptly employing users in existing posts within trusts, rather than putting them in supervised workshops for weeks or even months. This will show other employers that users can hold down competitive jobs.
Mentally ill women special needs and rights are stressed:

Double trouble

The duty of services to recognise the link between domestic violence and mental health (The Guardian, 13/08/2003)
The failure to recognise that domestic violence and mental health problems are often inextricably linked is not iso-

lated. There are concerns that mainstream mental health services are failing to pick up on the violence that lies behind some women presenting as mentally ill.
Even ethnic minorities rights are claimed:

Report 'details racism in NHS'

A report into the death of a schizophrenic man at a secure clinic [.] is expected to say that "institutional racism" is present across the NHS. (The Daily Mail- News section, 12/02/2004)
following the story of a:
Jamaican-born […] died in the […] Clinic, […] after being restrained by staff. […]. The report branded the treatment of members of the ethnic minorities by NHS mental health services "a disgrace" stating that: *institutional racism is present throughout the NHS* and that:
people from the black and minority ethnic communities who are involved in the mental health services are not getting the service they are entitled to.
Finally, dignity of clients of mental health services is defended in a number of items:

Watchdog condemns NHS trust over 'threadbare' services

Mentally ill patients and other local people were being put at risk due to its "failing" and "threadbare" mental health services (The Guardian, 16/03/2004) with special attention at compatibility with human dignity of clinical treatments and their appropriateness:

No holds barred

The use of straitjackets to control mental patients has long been discredited in Britain as inhumane and dangerous. (The Guardian, 02/02/2005)
Why has the NHS been examining whether to introduce controversial state-of-the-art mechanical restraints?
and at age groups specific needs:

Teenager was wrongly held in adult psychiatric unit

A teenager with severe learning difficulties was heavily sedated, sometimes forcibly, and locked up in an adult psychiatric unit for 18 months because a local council failed to fund an appropriate place for him (The Guardian, 02/02/2005)

Mental illness/psychiatric patient

A number of undifferentiated depictions imply that mental illness is a unitary condition, and encourage similar responses to anyone who suffers from such a disorder. An example is the well-known case of the man who tried to kill the former Beatle member George Harrison, a case where celebrity of people involved implies further sensationalism and hype.

Beatle's attacker is freed

George Harrison's widow said she felt 'dismayed and insulted' last night after the schizophrenic who tried to kill her late husband was released from a secure psychiatric unit. (The Daily Mail-News section, 05/07/2002)
In this note, the person's status as a patient was central, so that his mental illness was conveyed by systemic elements of the theme such as secure psychiatric unit, schizophrenic patient:
The schizophrenic patient who stabbed the Beatle ten times in the chest in a frenzied attack is now considered safe enough to be released even though he left the musician close to death.
Or mental health officials:
The decision by mental health officials to release […] comes amid heightened concern about the failings of the system to cope with people who are dangerously mentally ill.
Such systemic elements cue readers to make sense of the events by drawing on commonsense understandings that those who suffer from this condition (mental illness) are dangerous and unpredictable.
Other irrelevant diagnostic labels were added, with more stigmatization:
Former heroin addict Michael Abram was freed less than two years after being told he would be locked up indefinitely.
Another similar example can be cited from the Guardian:

Mentally ill stalker gets life for killing boy

A mentally ill man obsessed with child sacrifice was sentenced to life in prison yesterday for the murder of a boy of 12 in London (The Guardian, 02/02/2005), again by drawing on commonsense understandings that those mentally ill are dangerous and unpredictable.

Discussion

There are a number of methodological issues in relation to this study. The most important is the method of sample selection, including only a small non-representative sample of media items. Second, the sample was compiled retrospectively, from previously existing (which meant that it was impossible to operate with a specific definition of community care for the mentally ill) searchable databases that do not have a well-defined, and perhaps inaccurate, Boolean syntax. Thus, we may not have adequately search for positive elements in the depictions of community care for the mentally ill. This has important implications for the generalizability of findings.
Another important issue relates to the method of analysis used, content analysis procedures, to evaluate whether items were considered to be positive, neutral or negative, did not use any rating scale, and was purely subjective. However, the thematic analysis reliability was preserved

using a second investigator to seek consensus through an exhaustive discussion in the interpretation process. We also tried to temperate this limitation following the scheme of a classical relevant paper [12]. On a whole, there is a need to use triangulated methods. It is therefore difficult to interpret these findings, and we acknowledge that conclusions are tentative.

However, with regards to content analysis, the assessment of frequency showed that the overwhelming majority of items related to negative, violent representations. More than half of all items depicted care of the mentally ill within the community as dangerous. These depictions were more frequent for items from the Daily Mail, while the Guardian archive provided a larger amount of items related to the research question.

The thematic analysis identified four themes: risk of dangerousness and threat, vulnerability, human rights and mental illness/psychiatric patient. Three of these produced a stigmatizing depiction of the mentally ill and of related community care, adding strong criticism for psychiatric services. Risk of dangerousness and threat was foregrounded in news stories, encouraging feelings of disgust, outrage or fear of the patient, and of the people and institutions responsible for his presence in the community. The human rights theme offered the possibility of a positive depiction, although it is questionable whether this is able to achieve a positive portrayal of community care for the mentally ill. Many items where the vulnerability of the mentally ill in the community was emphasized actually undermined his/her entitlement to privacy and ordinariness. The characterization of community care seems sketchy and generic, largely because it is dominated by systemic elements of the mental illness/psychiatric patient theme, encouraging readers to draw on commonsense about mental illness in understanding the story. The portrayal of community care for the mentally ill as dangerous seems designed to capture the interest of readers. It is essential that readers are supported in ways that authorize their challenge to generic, depersonalized stereotypes of mental illness. The general population believes that psychiatric patients are unpredictable, and this belief may be influenced by the media [13 14].

Inappropriate language was a central concern, as along with particular framing devices, they may together contribute to the stigma associated with mental illness [15 16]. Other items reflected concerns, especially over government funding, government policies on mental health, and fears of funding cuts or shortages of services. The main concern is about printed media representations over a longer time frame. Such a choice is not an issue of accuracy or objectivity, but it does have serious ramifications for the ways in which audiences may interpret news and information about community care for the mentally ill, leading to accepting particular interpretations, such as, for example, seeing all people with a mental ill as violent and dangerous. If the right choices are made, they can help to destigmatize mental illness in the community and improve the lives of people with mental illnesses.

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Diagnosi precoce di nefropatia da litio

Early diagnosis of lithium-induced nephropathy

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Summary

Objectives

The aim of the study was to detect early markers of nephrotoxicity lithium-induced by blood test and ultrasound and magnetic resonance imaging (MRI). The nephrotoxicity effects of lithium are characterized by reduced urinary concentrating capacity wich can be detected as early as 8 weeks after lithium initiation. Nephrogenic diabetes insipidus is the most common adverse effect and occurs in up to 40% of patients.

Methods

To test the hypothesis, we enrolled twenty-six patients treated with lithium for more than one year and with one of the following symptoms or findings: polyuria-polydipsia, urine specific gravity < 1005, GFR < 90 ml/min/1.73 mq, proteinuria, hypertension. Patients underwent blood tests, urine NGAL, renal Doppler ultrasound and MRI in the presence of cysts.

Results

Of the twenty-six patients enrolled in the study ten had cysts and five had microcystic type cysts, pathognomonic of chronic tubulointerstitial nephritis. All patients with renal microcysts had a renal resistance index (RI) > 0.65. There were no correlations with NGAL.

Conclusions

According to data of IR index it is advisable to perform a renal Doppler ultrasound screening for patients treated with lithium as monitoring of renal function using only blood tests and urinary NGAL is insufficient. The practice guidelines of the American Psychiatric Association recommend measurement of serum creatinine level every 2-3 months during the first six months of lithium therapy and every year thereafter.

The decision to substitute lithium with another mood stabilizer raises a dilemma and should be made jointly by the patient, the psychiatrist and the nephrologist.

The issue is debated because the beneficial renal effect of lithium discontinuation might be observed, and not always, only in patients with moderate nephropathy. Maybe a point of no return exist, after which renal fibrosis continues to progress despite removal of the triggering insult.

Key words

Lithium • Nephrotoxicity • Renal microcysts

Introduzione

I sali di litio sono stati utilizzati come sostituti del sale fino a quando nel 1949 la *Food and Drug Administration* segnalò i rischi di intossicazione con effetti anche letali [1]. Successivamente si scoprì che il carbonato di litio possedeva effetti sedativi ed è stato utilizzato con successo nel trattamento della mania e nella profilassi dei disturbi bipolari. Tuttora il litio rimane il trattamento *gold-standard*, indicato come farmaco di prima scelta in tutte le linee-guida internazionali, per il trattamento e la profilassi del disturbo bipolare [2]. Il litio trova inoltre indicazione nel trattamento di altri disturbi dello spettro bipolare e nella depressione farmaco-resistente e vi sono prove di efficacia contro il rischio suicidiario e nel controllo dell'aggressività. Più recentemente il litio è stato anche utilizzato con risultati interessanti in ambito di ricerca nella malattia di Alzheimer [3] e nella sclerosi laterale amiotrofica [4].

La terapia con litio nel disturbo bipolare è una terapia che si protrae per un tempo indefinito, trattandosi di una patologia di tipo cronico ed essendo la sospensione del litio correlata a un elevato rischio di recidive e di peggioramento del decorso della malattia.

Tra i possibili eventi avversi legati all'assunzione del farmaco compaiono abbastanza frequentemente effetti collaterali neurologici (tremori), metabolici (ipotiroidismo e iperparatiroidismo), cardiaci (appiattimento o inversione dell'onda T) e renali. Gli effetti collaterali a livello renale si possono dividere in due categorie, a seconda del tempo di esposizione al farmaco.

1. *Precoci*: possono insorgere nelle prime settimane o nei primi mesi di trattamento l'acidosi metabolica e il diabete insipido nefrogeno (NDI) [5]. Il NDI è dovuto a

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un difetto di concentrazione urinaria, per resistenza all'ormone antidiuretico (ADH) [6], che determina sintomi di poliuria e polidipsia. Si tratta di una evenienza molto comune e potenzialmente reversibile, che interessa sino al 40% dei pazienti [7].

2. *Tardivi*: sono correlati a una esposizione protratta del farmaco l'ipercalcemia e la nefrite tubulo-interstiziale cronica (CTIN) che rappresenta un evento meno comune, ma grave perché rappresenta una patologia progressiva e porta allo stadio terminale dell'insufficienza renale, *End-Stage Renal Disease* (ESRD). La latenza media che intercorre tra l'inizio della terapia con litio e ESRD è di circa 20 anni [8].

L'effetto nefrotossico del litio è legato alla azione, dopo l'attraversamento della membrana citoplasmatica, di inibizione delle adenilciclasi e riduzione della sintesi dell'adenosina monofosfato (AMP) ciclico [9]. In conseguenza del ridotto stimolo, da parte dell'AMP ciclico, si altera la regolazione dell'antidiuresi per ridotta inserzione di acquaporina 2 nei canali del tubulo renale per il riassorbimento dell'acqua [10-12]. La nefropatia da litio tubulo-interstiziale cronica può evolvere insidiosamente in insufficienza renale cronica (CKD) con lieve o assente proteinuria [13].

I riscontri bioptici della nefrite tubulo interstiziale cronica (CTIN) includono atrofia tubulare e fibrosi interstiziale dove si trovano spesso delle cisti tubulari sia nella corticale sia nella midollare [14]. Le cisti tendono a essere sparse e sono microcisti, non eccedendo la dimensione di 1-2 mm di diametro [15].

Talora è presente una fibrosi pericistica con associato ispessimento della membrana basale tubulare cistica. Le cisti interessano il tubulo renale distale e il dotto collettore, mentre l'atrofia tubulare colpisce tutti e tre i segmenti del nefrone.

Nei pazienti in trattamento con litio è consigliato il periodico monitoraggio della funzionalità renale (creatininemia e *clearance* della creatinina [GFR]) che consente di minimizzare i rischi, ma non di evidenziare precocemente un quadro nefropatico. Recenti studi hanno mostrato che è possibile individuare precocemente la presenza di danni renali, anche di fronte a quadri paucisintomatici e ancora con reperti di laboratorio ai limiti della normalità [16 17]. Tali lesioni sono evidenziabili con una ecografia renale e/o con una risonanza magnetica (RMN) che mostrano immagini microcistiche patognomoniche della CTIN [18 19].

Materiali e metodi

Obiettivo dello studio

Lo studio si è posto l'obiettivo di valutare la funzionalità renale di pazienti in trattamento con litio attraverso esami ematochimici e strumentali per individuare quali fattori possono essere predittivi di compromissione renale al fine di una diagnosi precoce a livello preclinico e di una eventuale sospensione del farmaco per evitare la progressione della patologia renale.

Disegno dello studio

Si tratta di uno studio di tipo osservazionale di farmacosorveglianza. I soggetti sono stati reclutati nell'arco di tempo di 12 mesi tra i pazienti venuti a contatto presso le strutture ambulatoriali, ospedaliere e residenziali dell'Unità Operativa di Psichiatria, secondo i seguenti criteri.

Criteri di inclusione

Trattamento con litio da almeno 12 mesi

Presenza di almeno uno dei seguenti sintomi o reperti di laboratorio:

a. poliuria-polidipsia;
b. peso specifico urine < 1005;
c. GFR (velocità di filtrazione glomerulare) < 90 ml/min/1,73 mq;
d. proteinuria;
e. ipertensione arteriosa.

Criteri di esclusione

Nefropatie non litio-indotte.
Donne in gravidanza.

I pazienti che hanno accettato di aderire allo studio hanno dato il consenso informato in forma scritta.

Strumenti

I pazienti reclutati hanno eseguito esami emato-chimici (emocromo, elettroliti, funzionalità renale con grado CKD DOQI [*Kidney Disease Outcomes Quality Initiative*], litiemia) ed esami urine, compreso il biomarker neutrophil gelatinose-associated lipocalin (NGAL urinaria), indice di patologia tubulare [20].

Sono poi stati sottoposti a una un esame di I livello con ecografia renale B-mode e color-doppler per resistenze arteriose intrarenali (IR) con ecografo Esaote Lab 25.

Nel caso di riscontro di cisti renali all'esame ecografico si è eseguito un approfondimento diagnostico con esecuzione di risonanza magnetica, se non presenti controindicazioni (es. pazienti portatori di pace-maker).

Risultati

Sono stati arruolati nello studio 26 pazienti, di cui 17 femmine e 9 maschi, di età media pari a 52,7 anni. Nella

TABELLA I.
Diagnosi. *Diagnosis*.

ICD 10	Diagnosi	Numero di pazienti
F30-31	Disturbo bipolare	18
F25	Disturbo schizoaffettivo	4
F32-33	Depressione ricorrente	3
F23	Psicosi cicloide	1

Tabella I sono indicate le diagnosi dei pazienti secondo il sistema di classificazione ICD-10. Nella Tabella II sono indicati i dati socio-demografici e clinici.
In relazione alla stadiazione della nefropatia secondo i criteri DOQI dei 26 pazienti arruolati 8 sono risultati in Stadio 1 CKD con GFR > 90 con presenza di polidipsia-poliuria, 13 pazienti in stadio 2 con GFR 60-90, 4 pazienti in stadio 3 con GFR < 60 e 1 paziente in stadio 4 con GFR < 30.
All'esame ecografico si sono rilevati positivi per cisti renali 10 pazienti, di cui 5 presentavano microcisti tipiche di CTIN. Per la valutazione delle cisti renali si è utilizzato lo score di Farres [21].
Nelle Figure 1 e 2 sono visibili in sezioni sagittale e coronale le immagini cistiche caratteristiche della RMN renale di un paziente reclutato nel nostro studio.
Tutti i pazienti con microcisti renali tipiche avevano un l'indice di resistenza renale (IR) ≥ 0,65.
Non sono invece risultati indicativi di patologia renale i valori di lipocalina NGAL urinaria.
Nella Tabella III sono riportati i parametri di funzionalità renale, stadiazione DOQI e presenza di cisti per singolo paziente.

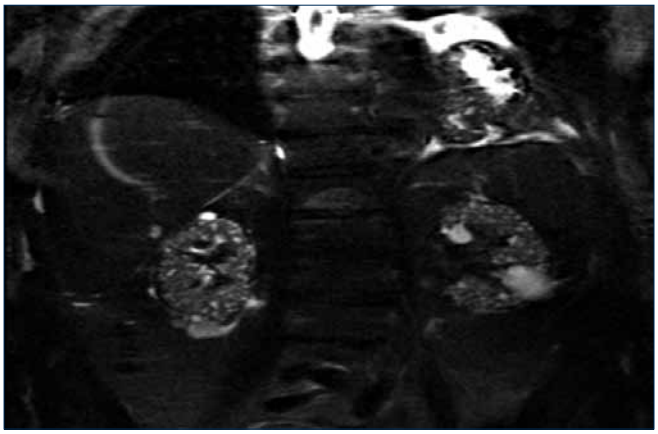

FIGURA 1.
RMN paziente con tipiche microcisti (sezione sagittale). *MRI in a patient shows typical microcysts (sagittal section).*

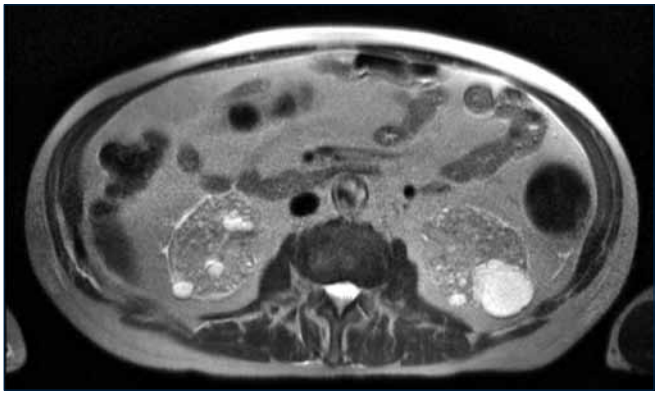

FIGURA 2.
RMN paziente con tipiche microcisti (sezione coronale). *MRI in a patient shows typical microcysts (coronal section).*

Discussione

La nefropatia da litio è una patologia a evoluzione tipicamente lenta e subdola, in quanto i primi sintomi possono essere del tutto non rilevati o sottovalutati dal paziente. La pressione arteriosa è infatti normale, il sedimento urinario può essere normale o con anomalie aspecifiche e la proteinuria assente o minima. L'unico fattore di rischio sinora dimostrato in letteratura è l'esposizione a lungo termine del farmaco. Sono stati ipotizzati come possibili fattori di rischio, ma con studi non sempre concordi, la plurisomministrazione giornaliera, l'utilizzo concomitante di altri farmaci nefrotossici, l'occorrenza di episodi di intossicazione acuta da litio, l'età avanzata e la comorbidità con ipertensione arteriosa, diabete mellito, iperuricemia e iperparatiroidismo [22 23]. Non sono state dimostrate correlazioni con il dosaggio giornaliero del litio né con la litiemia.
Non esistono evidenze sistematiche sulle quali basare la decisione di interrompere la terapia con litio, particolar-

TABELLA II.
Dati demografici e clinici. *Demographic and clinical data*.

	Età (sd)	M/F (%)	Durata trattamento anni (sd)	Litiemia (sd)
Media	52,7 (13,52)	65/35	14,3 (8,63)	0,52 (0,18)
Range	32-76		2-35	0,3-1,0

TABELLA III.
Funzionalità renale e stadiazione per singolo paziente: vengono riportati di ogni paziente i valori di velocità di filtrazione glomerulare (GFR), la stadiazione del danno renale (CKD), l'indice di resistenza renale (IR) e la presenza di cisti da rilievo ecografico e di microcisti all'immagine RMN. *Renal function and staging for each patient: glomerular filtration rate (GFR), staging renal disease, renal resistance index (IR) and presence of cysts and microcysts.*

Paziente	GFR ml/min/1,73mq	Stadio CKD	IR renali	Cisti	RMN	Microcisti
1	16	4	0,78	Sì	Sì	Sì
2	32	3	0,80	Sì	No	Sì
3	52	3	0,71	Sì	Sì	Sì
4	56	3	0,65	Sì	Sì	Sì
5	58	3	0,625	No		
6	60	2	0,665	No		
7	64	2	0,685	No		
8	65	2	0,63	No		
9	66	2	0,665	Sì	Sì	No
10	68	2	0,565	No		
11	70	2	0,61	No		
12	74	2	0,67	No		
13	77	2	0,66	Sì	Sì	Sì
14	78	2	0,59	No		
15	80	2	0,64	No		
16	84	2	0,65	No		
17	86	2	0,59	No		
18	87	2	0,61	Sì	Sì	No
19	>90	1	0,67	No		
20	>90	1	0,645	No		
21	>90	1	0,645	No		
22	>90	1	0,64	Sì	No	No
23	>90	1	0,64	No		
24	>90	1	0,65	No		
25	>90	1	0,53	Sì	Sì	No
26	>90	1	0,66	Sì	Sì	No

mente per moderati gradi di insufficienza renale cronica. Le raccomandazioni dell'*American Psychiatric Association* prevedono un controllo della creatininemia 3 volte nel primo semestre di trattamento e successivamente ogni anno [24].

Quando la velocità di filtrazione glomerulare (GFR) è < 60 ml/min/1,73 mq (CKD stadio 3) andrebbero effettuate indagini di approfondimento nefrologico. Tuttavia tale segno, *pur importante da monitorare anche perché semplice e poco costoso* è già indicatore di un danno renale avanzato e ha scarso rilievo in termini di intervento precoce [25].

Considerato che la presenza di microcisti renali nella nostra casistica è presente nel 7,7% di CKD in stadio 2 oltre che nel 75% in stadio 3 e nel 100% in stadio 4 e che l'IR > 0,65 correla con la presenza di microcisti renali, lo studio ecocolordoppler renale *e l'eventuale approfondimento RMN risultano strumenti utili nel monitoraggio* di tali pazienti per l'individuazione precoce delle situazioni a rischio. *Anche se nessuno degli strumenti utilizzati ha una capacità predittiva specifica*.

Il nostro studio, anche se effettuato su una casistica limitata di pazienti, ha messo in evidenza come il rischio di sviluppare condizioni di nefrotossicità da litio sia tutt'altro che remoto. Un'accurata valutazione della bilancia rischi/benefici si impone in questi pazienti, e se la sospensione del litio è sicuramente rischiosa, altrettanto lo

è quella di indurre situazioni irreversibili di nefrotossicità. Purtroppo allo stato attuale mancano indicatori precisi a sostegno dell'indicazione a sospendere il trattamento con litio, e anche la decisione di sostituire il litio con un altro stabilizzatore dell'umore rimane una scelta difficile e problematica, che va definita in accordo con il paziente e in sinergia tra psichiatra e nefrologo. La sospensione del litio, che resta il farmaco di prima scelta nel trattamento del disturbo bipolare, può determinare infatti delle recidive del disturbo con connessi rischi anche di mortalità per suicidio. Dall'altro lato non sempre l'interruzione del litio determina una regressione o un arresto del danno renale. Esiste probabilmente un punto di non ritorno oltre il quale la fibrosi renale continua a progredire nonostante la rimozione dell'agente lesivo.
Riteniamo opportuni ulteriori studi di controllo nefrologico dei pazienti esposti ad anni di trattamento con litio a conferma delle nostre osservazioni.

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Epidemiology of suicide attempts in a psychiatric setting in Northern Italy

Epidemiologia dei tentati suicidi in un Servizio di Salute Mentale del Nord Italia (Rovigo)

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Summary

Objectives

An observational study was carried out to investigate suicide attempts in the period from January 1, 2006 to December 31, 2010 in the population of legal age from the territory of Rovigo in Northern Italy.

Methods

All intentional self-poisoning or self-injury events, irrespective of motivation, that came to the attention of Mental Health Services was recorded. Personal data (age, sex, marital status, occupation, educational level and family composition), clinical data (main diagnostic group, method used in the attempt, previous contact with the Service, previous suicide attempts, site of first psychiatric consultation) were recorded for every person encountered by the psychiatrist involved in the first evaluation. All the people recruited were also asked to fill in a self-administered interview composed of three questionnaires: QD - questionnaire of depression by CBA – cognitive behavioral assessment; BSI – borderline syndrome index and RFL – reason for living inventory.

Results

Two-hundred and sixty-five suicide attempts with a psychiatric evaluation were considered in a population of 149,300 people over a period of 5 years. A higher distribution in females and younger people was found. There is a high percentage of unemployed people (23.1%), especially among males (29.3%) (χ^2 test:4.02; $p < .05$). In the majority of cases the means of the suicidal attempt is drug poisoning (59%) and violent methods (hanging, gas poisoning, jumping, fire arms and drowning) represent the 25.2% of all the sample, with a higher percentage for male subjects (35.9%; OR: 2.66 [95% CI: 1.34-5.29]). The great majority of people were assessed in Emergency Rooms (64.1%) and after the psychiatric evaluation, 69.2% of the people were hospitalized in psychiatric wards. The main diagnostic group is personality disorders (33.3%) followed by mood disorders (24.4%): there is a significant sex difference with more females with mood disorders (χ^2 test: 6.88; $p < .01$) and more males with alcohol/substance disorders (χ^2 test: 19.4; $p < .01$). In 40.6% of cases had at least one contact with Mental Health Services before while a relevant percentage of people (43.2%) had a positive history for previous attempts. People with a positive history of suicidal attempts were at major risk of borderline personality (OR: 2.01 [95% CI: 1.02-3.95]) while it was less evident in people with a higher presence of reason for living by the RFL questionnaire ($p < 0.05$; adjusted OR: 0.39 [95% CI: 0.16-0.94]).

Conclusions

The findings confirm data in the literature on suicide attempts in Western populations and provide the state of the art at the local and national level. The investigation stresses the established evidence that a large proportion of suicide attempters do not pertain to the population usually served by Mental Health facilities. It also suggests a possible discrimination of different profiles among those attempting suicide. Some indications for future prevention planning emerge: it is possible to differentiate two levels of prevention with a "selected prevention" on males, unemployed individuals and those who do not come to the attention of mental health professionals, and an "indicated prevention" for patients with a positive history of suicidal attempts.

Key words

Suicide-attempt • Epidemiology • Mental-Health Service

Introduction

Suicidal behaviour, spanning from self-harm without injuries to completed suicide [1], is recognized as a serious public health problem [2]. In Europe, suicide is one of the first three causes of death in 15- to 44-year-old individuals [3]. Italian data from 2007 show 6.3 suicides every 100,000 inhabitants per year [4], with a larger number in Northern regions [5]. The rates in Italy decreased from 1980 to 2002, and at the same time an increasing use of highly lethal methods was observed [6].

Epidemiological data show two patterns considering suicide attempts or completed suicides. A clear-cut difference emerges on incidence, age/sex distribution and methods of attempts, but the major risk factors are common: lack

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of an affective relationship, changes in living situation or living in an institution, unemployment, mental disorder, alcohol or substance abuse, low socio-economic status and previous suicide attempts [7].

The greatest predictor of eventual suicide is a personal history of suicide attempts [8], which can be found in about 40% of suicides [9]. The relative risk is much higher in the first year, but remains significantly high even after 15 years [10]. The rate of suicide attempts is considered to be at least 10 times that of suicide [11], but its estimation is inaccurate as national registers are available only for suicide cases. The majority of cases do not come to the attention of Health Services, and many remain unknown even to relatives and friends. In a pyramidal projection, the proportion of attempts seen by Mental Health Services is located on the top [12].

In Italy, the data show a rate of suicidal behaviour (included suicide attempts) that is lower than that registered in Northern Europe, and in line with the Mediterranean area [13]. A study performed in Padua (Veneto-Italy) in hospital-admitted subjects found a rate ranging from 59.2 to 93.6 per 100,000/year considering two different periods: 1992-1996 and 2002-2006, respectively [14]. In a previous study carried out by our group, a rate of 36.4 per 100,000/year was estimated in individuals admitted to the general hospital of Rovigo (Veneto-Italy) for parasuicide acts [15]. To date, these investigations account for the literature on the epidemiology of suicide attempts in Italy.

An observational population-based study was carried out to investigate suicide attempts in the five-year period from January 1, 2006 to December 31, 2010. The population of this study consisted of the residents of legal age (≥ 18-year olds) from the territory of Rovigo's Public Health Unit. On December 31, 2009 they numbered 149,300, while the entire population was 175,129. This territory is located in the Veneto region in the North of Italy and is a rural area with prevailing agricultural and small industrial activities; its population density is 175/km^2, and the proportion of elderly people is significantly higher than that in Italy. In the Rovigo area, a suicide rate of 11.7 cases/100,000/year was recorded during the period from 1999-2007 [16].

Methods

The sample consists of suicide attempts (during the period 2006-2010) by residents of legal age (≥ 18-year-olds) from the area of the Local Health Authority that were assessed with psychiatric evaluation. Each intentional self-poisoning or self-injury, irrespective of motivation, that came to the attention of Mental Health Services (i.e. people that committed a suicide attempt and after that were referred to a psychiatrist for an evaluation) was recorded, and individuals were asked to participate in the study. Personal data (age, sex, marital status, occupation, educational level and family composition), clinical data (main diagnostic group, method used in the attempt, previous contact with the Service, previous suicide attempts, site of first psychiatric consultation) were recorded for each participant encountered by the psychiatrist in the first evaluation. All individuals recruited were also asked to complete a self-administered interview composed of three questionnaires: QD (*Questionnaire of Depression*) by CBA (*Cognitive Behavioral Assessment*, Italian version) [17] with a cut-off of 15 or more in a 24-item scale; BSI (*Borderline Syndrome Index*) [18] with a cut-off of 24 or more in a 52-item scale; RFL (*Reason For Living Inventory*) [19], with a total score plus 5 factors scores, that are obtained with the average of all the responses in a Likert-scale from 1 to 6 (from the lowest to the maximum of reason for living). For this latter questionnaire, scores of more than 3.50 were considered positive for a presence of reasons for living. Due to the relatively small sample, it was taken into account only the RFL-total score. The Paykel scale for recent life-events was also recorded [20]. Questionnaires were chosen on a practical basis: they are all self-administered, and relatively easy and quick to use. They were collected in the psychiatric ward or the out-patient centre by a nurse previously trained to assist patients in completing the questionnaires.

Data were summarized as frequencies and percentages for categorical data (and as means ± SD for continuous data). The incidence rate was estimated considering the average number for one year of all cases encountered and referred to the population of legal age (≥ 18-year-olds) from the territory of Rovigo's Public Health Unit. Analyses were performed using a χ^2 test or Fisher's exact test, and Student's t-test as appropriate. A p value of $p < 0.05$ was considered significant (and odds ratio [OR] with a 95% confidence interval [CI] was calculated). A multivariate logistic regression analysis was carried out to determine variables that were independently associated with repetition of attempts, use of violent methods and outcomes by psychometric questionnaires. Due to the small sample (n = 150), some variables were aggregated in less categories for the analysis of questionnaires. Analyses were performed using the Statistical Package for the Social Sciences (SPSS ver. 18, Chicago, Illinois, USA). All participants were informed about the nature of the study, and in particular that data would be aggregated in anonymous manner.

Results

The total number of suicide attempts during the five year period was 265, recorded in 234 subjects; 21 repeated the act several times with an average of 2.48 acts per person. The average rate of suicide attempts per year

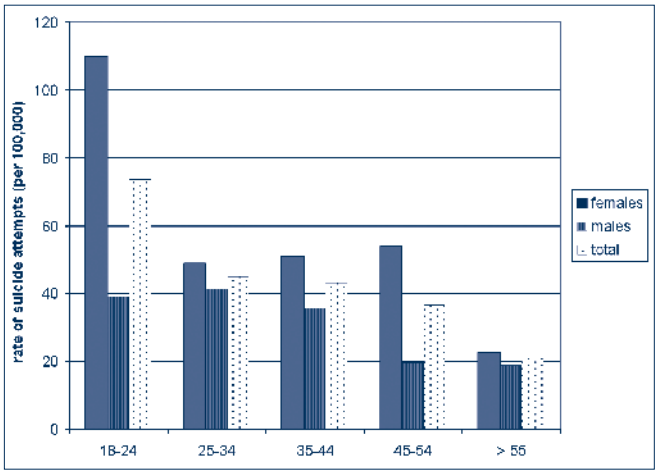

FIGURA 1.
Incidence by age and sex (cases per 100,000/year) of suicide attempts seen by the Mental Health Service of Rovigo (period 2006/10). *Tassi per età e sesso dei casi (per 100.000 abitanti/anno) di tentati suicidi visti dal Dipartimento di Salute Mentale di Rovigo nel periodo 2006/10.*

was 53, and thus the estimated incidence was 35.5 cases/100,000/year (referred to legal age population of the area, corresponding to 149,300 people).
There were 92 males with 99 acts (37.36%) and 142 females with 166 acts (62.64%) with an average age of 43.94 (± 16.80) and no differences between males and females (Student's t-test: 0.28; p = 0.77). The incidence rate referred to the population was 42.7 cases/100,000/year for females and 27.7 cases/100,000/year for males. As shown in Figure 1, the rate of suicide attempts decreases with age, and this was particularly true for females (in age range 18-24 years a rate of 110.1 cases/100,000/year was found for females).
Considering marital status, the majority (59.4%) were unmarried (single, divorced or widowed), and this was more evident for males than females (χ^2 test: 4.13; $p < 0.05$). In 77.8% of the sample a low school grade had been achieved (up to 8 years of education). There was a high percentage of unemployed individuals (23.1%), especially among males (29.3%) (χ^2 test: 4.02; $p < 0.05$), and people in non-professional conditions (students, housewives and retired) (35.0%) (Table I).
In the majority of cases, the means of the suicidal attempt was drug poisoning (59%), followed by self harm by cutting oneself with sharpened objects (10.7%); less frequently attempts were carried out by hanging (6.4%), gas poisoning (5.6%) and poisoning with chemical products (5.1%). Overall, violent methods (hanging, gas poisoning, jumping, fire arms and drowning) represented 25.2% of the sample, with a higher percentage for male subjects (35.9% with violent methods). The large majority of people were assessed in Emergency Rooms (64.1%); 14.1% of the sample consisted of people who referred directly to Mental Health out-patient facilities. After psychiatric evaluation, 69.2% of those were hospitalized in psychiatric wards. A third were diagnosed with personality disorders (diagnosis recorded in patients' files), representing the main diagnostic group, followed by mood disorders (24.4%) and adjustment disorders (18.4%). There was a significant gender difference with more females with mood disorders (χ^2 test: 6.88; $p < 0.01$), and more males with alcohol/substance disorders (χ^2 test: 19.4; $p < 0.01$). 40.6% of cases had at least one contact with Mental Health Services before the evaluation related to the suicide attempt; therefore, about 60% of people who had attempted suicide were new cases for Mental Health Service. A relevant percentage of people (43.2%) had a positive history for previous attempts (Table I).
One hundred and fifty people were assessed with psychometric questionnaires. The main reasons for not completing the questionnaires were drop-outs (37%) and patient refusals (31%). The distribution of this population (n = 150) was different from the entire sample with regard to three variables: people who completed the investigation with psychometric questionnaires had a higher educational level (χ^2 test: 6.58; $p < 0.01$), more frequently hospitalized (χ^2 test: 4.46; $p < 0.05$), and a diagnosis of mood disorders was more frequent (χ^2 test: 6.46; $p < 0.05$). In this sample, 38.3% was positive for depressive symptoms by the QD questionnaire, and 46.1% had higher score by the BSI questionnaire. Reasons for living (RFL questionnaire) were found in 53.2% of the sample. The Paykel scale accounts for stressful life events in the past six-months, and four of five subjects reported at least one stressful event; the majority reported a single event (72.7%).
Logistic multivariate analysis with dependent variable "violent methods" versus "non-violent methods" revealed a statistically significant correlation: men were at higher risk for using violent methods ($p < 0.01$; adjusted OR: 2.66 [95% CI: 1.34-5.29]). There was also a slight trend (although it did not reach statistical significance) for correlation between violent methods and unemployment condition. Logistic multivariate analysis with dependent variable "repetition of attempts" showed a statistically significant correlation ($p < 0.01$; adjusted OR: 3.50 [95% CI: 1.85-6.62]) with previous contacts with Mental Health Services. Logistic multivariate analysis revealed that those subjects with a major presence of depressive symptoms by the QD questionnaire were less frequently hospitalized ($p < 0.05$; adjusted OR: 2.82 [95% CI: 1.15-5.88]), while those with more reasons of living by the RFL questionnaire have more probability of not being hospitalized ($p < 0.05$; adjusted OR: 0.36 [95% CI: 0.14-0.89]). A positive history of previous attempts corre-

TABLE I.
Personal and clinical data (with percentage of distribution) of 234 subjects with a suicide attempt that were assessed by the Mental Health Service of Rovigo (periodo 2006/10) [*in bold, the statistically significant differences between sexes*]. *Dati socio-demografici e clinici (con relative percentuali) dei 234 soggetti con un tentato suicidio valutati dal Dipartimento di Salute Mentale di Rovigo nel periodo 2006/10 [in grassetto, le differenze statisticamente significative tra i sessi].*

Variable		Sex				Total (n = 234)	
		Females (n = 142)		Males (n = 92)			
		n	(%)	n	(%)	n	(%)
Age range							
	< 24	22	(15.5)	10	(10.9)	32	(13.7)
	25-34	26	(18.3)	20	(21.7)	46	(19.7)
	35-44	29	(20.4)	24	(26.1)	53	(22.6)
	45-54	32	(22.5)	13	(14.1)	45	(19.2)
	> 55	33	(23.2)	25	(27.2)	58	(24.8)
Marital status							
	Married	60	(42.3)	27	(29.3)	87	(37.2)
	Not-married	**77**	**(54.2)**	**62**	**(67.4)**	139	(59.4)
	N. A.	5	(3.5)	3	(3.3)	8	(3.4)
Educational level							
	Lower (up to 8 years)	109	(76.8)	73	(79.3)	182	(77.8)
	Upper	28	(19.7)	16	(17.4)	44	(18.8)
	N. A.	5	(3.5)	3	(3.3)	8	(3.4)
Professional condition							
	Working	45	(31.7)	31	(33.7)	76	(32.5)
	Not-professional	57	(40.1)	25	(27.2)	82	(35.0)
	Unemployed	**27**	**(19.0)**	**27**	**(29.3)**	54	(23.1)
	N. A.	7	(4.9)	2	(2.2)	9	(3.8)
First assessment							
	Emergency room	97	(68.3)	53	(57.6)	150	(64.1)
	Psychiatric out-patients facilities	20	(14.1)	13	(14.1)	33	(14.1)
	Intensive care	11	(7.8)	14	(15.2)	25	(10.7)
	Other hospital Dpts	7	(4.9)	4	(4.4)	11	(4.7)
	Home	7	(4.9)	8	(8.7)	15	(6.4)
Psychiatric hospitalization after the suicide attempt							
	No	50	(35.2)	22	(23.9)	72	(30.8)
	Yes	92	(64.8)	70	(76.1)	162	(69.2)
Clinical diagnosis							
	Mood disorders	**43**	**(30.3)**	**14**	**(15.2)**	57	(24.4)
	Personality disorders	51	(35.9)	27	(29.3)	78	(33.3)
	Psychosis	10	(7.0)	10	(10.9)	20	(8.5)
	Adjustment disorders	26	(18.3)	17	(18.5)	43	(18.4)
	Alcohol/substance disorders	**5**	**(3.5)**	**20**	**(21.7)**	25	(10.7)
	Dementias	4	(2.8)	2	(2.2)	6	(2.6)
	Mental retardation	3	(2.1)	2	(2.2)	5	(2.1)
Previous contact with Mental Health Services							
	No	84	(59.2)	55	(59.8)	139	(59.4)
	Yes	58	(40.8)	37	(40.2)	95	(40.6)

(continues)

(Table I follows)

Variable		Sex				Total (n = 234)	
		Females (n = 142)		Males (n = 92)			
		n	(%)	n	(%)	n	(%)
Method used							
	Drug poisoning	95	(66.9)	43	(46.7)	138	(59.0)
	Self-harm with sharpened objects	14	(9.9)	11	(12.0)	25	(10.7)
	Gas poisoning	4	(2.8)	9	(9.8)	13	(5.6)
	Fire arms	1	(0.7)	3	(3.3)	4	(1.7)
	Hanging	4	(2.8)	11	(12.0)	15	(6.4)
	Jumping	6	(4.2)	4	(4.3)	10	(4.3)
	Chemical products	6	(4.2)	4	(4.3)	10	(4.3)
	Drowning	9	(6.3)	3	(3.3)	12	(5.1)
	Others	23	(2.1)	4	(4.4)	7	(3.0)
Violent methods							
	No	116	(81.7)	59	(64.1)	175	(74.8)
	Yes	**26**	**(18.3)**	**33**	**(35.9)**	59	(25.2)
Previous attempts							
	No	77	(54.2)	56	(60.9)	133	(56.8)
	Yes	65	(45.8)	36	(39.1)	101	(43.2)

lates with borderline symptoms by the BSI questionnaire ($p < 0.05$; adjusted OR: 2.01 [95% CI: 1.02-3.95]), while it was less evident in people with a higher presence of reason for living by the RFL questionnaire ($p < 0.05$; adjusted OR: 0.39 [95% CI: 0.16-0.94]).

Discussion

The well-established findings in the literature are confirmed by the present study in the area of Rovigo (Northern Italy). Suicide attempts were more common in females and younger people [13]. A high frequency of unemployment, non-married status (single, widowed or divorced), and low educational level were more common [21-23]. Considering that in the Veneto region unemployment rates fluctuated between 3.3% and 5.8% during the years of the study [24], the present sample is characterized by at least 4 times the unemployment rate of the general population. Some gender differences were found: males were more frequently unmarried and unemployed; they had been diagnosed less frequently with mood disorders, but more frequently with alcohol/substance disorders and were more prone to use violent methods. These data suggest different profiles for attempters: males were more influenced by social conditions and alcohol while considering to take their own lives. The choice for violent methods by males and the association between lethality of method and intention to die find conflicting data in literature [25 26]. More than 70% of suicide attempters acknowledged stressful life events in the preceding six months. This, associated with the fact that the majority of people (n = 139; 59.4%) were at their first contact with mental health professionals, brings attention to a phenomenon that appears crisis-like [27 28]. This interpretation is reinforced by the relative low presence of major psychiatric disorders: there was a considerable proportion of adjustment disorders (n = 43; 18.4%) and alcohol/substance disorders (n = 25; 10.7%). In addition, the major diagnostic group is represented by personality disorders, which is frequently an inaccurate diagnosis [29] and has a poor stability over time [30]. Since suicide attempts tend to repeat and are highly associated with the risk of completed suicide [7], the challenge for preventive strategies is to reach those people in crisis without social support and without a help-seeking attitude [31].

There was a considerable proportion of subjects (n = 101; 43.2%) with a positive history of suicidal attempts. The individuals are at major risk of having a borderline personality (BSI questionnaire) and less willingness to live (RFL questionnaire), but are more likely to attend Mental Health Services. People with previous attempts represent a sub-population with poorer psychological balance, which suggests a dedicated prevention in this group [32 33]. Subjects who were hospitalized after the attempt had a lower perception of depressive symptoms by the QD questionnaire and a higher motivation to live using the RFL questionnaire. This was an unexpected outcome, although one possible explanation is that the situation influenced the responses, especially with self-administered questionnaires. One hypothesis is that non-hospitalized individuals might have a poorer perception of their psychological status in the aftermath of a suicidal crisis. An-

other explanation is that psychiatrists considered not only psychopathology in their evaluations, and therefore decided to admit people with other risk factors (e.g., low social support) to the psychiatric ward. While questioning the psychometric power of the questionnaires used, these results strengthen the outcomes of multivariate analysis in subjects with previous attempts (see above).

The major limitation of this study is that the population of the present work pertains only to a portion of all suicide attempts. Considering the population of legal age of the area, an incidence of 35.5 suicide attempts per 100,000/year can be estimated: taking into account that the suicide rate in the entire population of the area is 11.7 cases/100,000/year, the proportion found is far from that indicated in literature (at least 10 suicide attempts for every suicide) [11]. Nevertheless, a comparison might be made with two studies from the nearby area of Padua [14], considering that they are geographically and culturally close and have similar demographical features. The incidence found in the periods 1992-1996 and 2002-2006 was 59.2 and 93.6 cases/100,000/year, respectively: in both cases, the samples were all represented by suicide attempts referred to a general hospital, irrespective of any psychiatric evaluation. In a previous work of our group, an incidence of 36.4 parasuicides presented to the general hospital (per 100,000/year) was found: this was a retrospective study on medical electronic files, with all the possible biases and missing data for this kind of investigation [15]. Another limitation of the present work is represented by the different distribution of the people that completed psychometric evaluation. This fact prevents us from generalizing the results of the questionnaires to the entire sample. It also gives more weight to the impossibility to know how people that do not come to the attention of mental health professionals would have resulted in the variables explored. Moreover, while we found some interesting data related to violent methods, the actual lethality was not assessed.

Despite the above limitations, the present investigation stresses the established evidence that a large proportion of suicide attempters do not pertain to the population usually served by Mental Health facilities. It also suggests a possible discrimination of different profiles among those attempting suicide. Social factors may play a role in addition to mental disorders and psychological pain. This is confirmed by the limited function of psychometric tools in assessing risk. A sub-population of people with a tendency to repeat suicidal acts could also be highlighted. Considering these data, some indications for prevention programmes emerge. As suggested by Nordentoft [34], it is possible to differentiate two levels of prevention: *selected prevention* on males, unemployed individuals and those who do not come to the attention of mental health professionals, and *indicated prevention* for patients with a positive history of suicidal attempts. While this latter strategy can be limited to specialist settings, selected prevention needs multiple contributions and large-scale projects involving different territorial agencies [35 36].

In conclusion, the present findings confirm the data in the established literature on suicide attempts in Western populations [7 37], and provide the state of the art at local and national level and give indications for future prevention planning.

Acknowledgements

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Uno studio pilota sulla qualità della vita in pazienti con sclerosi multipla

Quality of life in patients with multiple sclerosis: a pilot study

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Summary

Objectives

The evaluation of health in relation to quality of life (Health Related Quality of Life-HRQOL) is a measure of the general quality of the life of a subject. It encompasses several areas: the state of health, both physical and psychological, social functioning, and it can also measure impairments, symptoms and disabilities. It is a measure of the individual perception of the functional role, social health and general comfort, as well as the sexual functioning and personal satisfaction of the individual. The symptom "sense of fatigue" has been taken into consideration because of its particular onset, in the manifestation (to completely disable a subject) and in incidence to determine its impact on quality of life. The measure of the quality of life helps to provide a broad quantification of the impact on the illness and to develop a programme of care that can satisfy the patient's needs.

Methods

The study cohort consisted of 32 patients with a confirmed diagnosis of multiple sclerosis. The criteria for inclusion were: attending a rehabilitative centre for periodic psychiatric visits or physiotherapy; an EDSS < 7 (this is useful indicator of the global measure of the level of disability in a patient); informed consent for participation.

All subjects were administered two tests: the Multiple Sclerosis Quality of Life Test (MSQOL-54) and the Modified Fatigue Impact Test Scales (MFIS), based on items derived from interviews with patients with multiple sclerosis that describe how fatigue influences their life.

Results

The study population was heterogeneous. The results showed that a decrease in QoL corresponds to alteration of the "sense of fatigue". This causes damage to physical and mental functioning of health.

The high EDSS score is related to alteration of physical functioning, increased emotional well-being and cognitive function.

Considering the age of subjects with multiple sclerosis, it would appear that increased age decreases physical and sexual functions, but without any other differences in the other functions measured. The duration of illness has more influence on the quality of life than age.

Moreover, the years after the onset of the illness are related with some aspects of the QoL, particularly with cognitive function which seems to increase together with the number of years from diagnosis, whereas they are related to a decrease in physical functioning.

Conclusions

Change in behaviour in individuals with multiple sclerosis was observed both by patients and family, and these changes influence QoL in reference to mental health and physical and social functioning.

Measures of QoL may be useful to assess the results of specific medical treatments. This is important since individualization of the risk of worsening of the state of health due to deterioration in physical and mental functions has psychological alterations such as the loss of identity, disesteem, sense of impotence, lack of independence, loss of personal control and fear of the future, which often leads to major depression.

Key words

Multiple Sclerosis • Quality of life (QoL) • Multiple Sclerosis Quality of life-54 (MSQOL-54) • Modified Fatigue Impact Test Scales (MFIS) • EDSS • Sense of fatigue • Disability • Cognitive functioning • Physical functioning

Introduzione

L'Organizzazione Mondiale della Sanità (OMS) definisce la salute come uno stato di completo benessere fisico, mentale e sociale e non semplicemente come assenza di malattia [1]. Si assiste quindi, con il nuovo millennio, a un netto cambiamento del modello biomedico tradizionale che poneva attenzione solo sulle cause biologiche trascurando il fatto che la maggior parte delle malattie è il risultato di un'interazione di fattori sociali, psicologici e biologici. Nello studio condotto da Kaplan [2], si è messo a confronto il modello biomedico tradizionale con il "modello outcomes" la cui differenza riguarda il valore posto sull'autovalutazione del paziente: mentre il primo enfatizza la patologia e il loro trattamento, il secondo valuta i vantaggi in termini di qualità d'adattamento alla vita negli anni (*Quality-Adjusted Life Years*, QOLYs). Molti adulti

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continuano a soffrire della loro malattia, convivendo con la loro disabilità per lunghi anni e nonostante continuino a vivere, la loro qualità della vita è peggiorata.
Un numero diverso di fattori può migliorare l'impatto e l'adattamento alle malattie croniche, questi includono: la personalità dei pazienti, precedenti esperienze di eventi simili, la natura progressiva della malattia, il livello di sostegno e la percezione di sé. Questi sono gli aspetti in grado di migliorare le strategie del paziente con conseguenze sull'impatto della malattia sul funzionamento psicosociale dello stesso [3].
La sclerosi multipla (SM) o sclerosi in placche è una patologia a esordio acuto o subacuto, ad andamento remittente-recidivante, caratterizzata da demielinizzazione a placche sparse nel sistema nervoso centrale (SNC). Tale perdita di mielina è accompagnata da una alterazione dell'abilità dei nervi a condurre gli impulsi elettrici da e per il cervello e questa alterazione produce i vari sintomi presenti nella SM. Le aree in cui si verifica la perdita della mielina (placche o lesioni) appaiono come aree indurite (cicatrici): nella SM queste cicatrici appaiono in tempi e in aree diverse del cervello e del midollo cerebrale, provocando così lo spettro sintomatologico tipico della malattia.
Sul piano clinico la SM è caratterizzata dalla notevole poliedricità dei sintomi, peraltro rispecchiante la variabilità della localizzazione e dell'estensione della lesione anatomo-patologica fondamentale, ovvero la placca di demielinizzazione.
L'andamento bizzarro di questa malattia, curabile ma non guaribile, di cui non conosciamo esattamente le cause e in cui le riacutizzazioni e le remissioni e anche il grado di disabilità raggiungibile a lungo termine sono sostanzialmente imprevedibili, rendono impossibile un giudizio prognostico sulla futura qualità della vita del paziente. Pertanto, ricevere la diagnosi di SM rende ragione della riconsiderazione del progetto esistenziale anche nell'entourage del paziente e della potenziale comparsa di disturbi della sfera psichica.
Le forme che questa malattia può assumere sono diverse: dalla forma recidivante-remittente, in cui ci sono recidive imprevedibili (esacerbazioni, attacchi) durante le quali appaiono nuovi sintomi oppure i sintomi già presenti diventano più severi; alla forma progressiva primaria, caratterizzata dalla mancanza di attacchi distinti ciò nonostante l'esordio è lento, il peggioramento dei sintomi è costante. Vi è un accumulo di deficit e di disabilità che a un certo punto può stabilizzarsi oppure continuare per diversi mesi o anni; alla forma progressiva secondaria, in cui inizialmente il paziente è affetto da SM recidivante-remittente, durante il corso della malattia si sviluppano disabilità progressive, spesso con la sovrapposizione di recidive; sino alla forma benigna, in cui dopo uno o due attacchi con recupero completo, il quadro clinico non peggiora col tempo e non vi è disabilità permanente.
Mentre il quadro clinico relativo ai disturbi fisici della malattia è noto da molto tempo, gli aspetti psicologici e neuro comportamentali hanno visto un serio approfondimento scientifico solo nel corso degli ultimi quindici anni.
Molti dei sintomi associati con la SM sono soggettivi pertanto c'è una difficoltà di misura, in particolar modo per i sintomi sensoriali e la fatica. Alcuni sintomi possono anche essere transitori e non vengono scoperti durante gli esami di routine neurologici. L'*Expanded Disability Status Scales* (EDSS) [4], rappresenta una misura globale di *impairment* e di *disability* il cui punteggio varia, attraverso incrementi di 0,5 punti, da 0 (esame neurologico normale) a 10 (morte per SM), viene usato per valutare la disabilità di base nella SM è probabilmente il migliore strumento usato in questo contesto.
C'è un aumento d'interesse sulla salute relativa alla qualità della vita (*Health Related Quality of Life*, HRQoL) in letteratura medica degli ultimi anni. L'HRQoL include alcuni importanti campi della salute: il benessere dell'essere umano, le funzioni sociali e le funzioni psicologiche che non sono direttamente connesse con l'indebolimento neurologico e la malattia, invece, vengono considerate dai pazienti essere più importanti (determinanti) del loro complessivo stato di salute di quanto lo sono il danneggiamento delle funzioni fisiche.
Recentemente sono state sviluppate misure che includono la valutazione cognitiva, dell'umore, della funzione sessuale e della fatica [5]. L'HRQoL è una misura che ingloba campi molteplici e generalmente coinvolge la percezione propria del paziente. Include lo stato di salute, fisico e psicologico, il funzionamento sociale e può anche misurare le menomazioni, i sintomi o le disabilità. È una misura della percezione individuale del ruolo funzionale, della salute sociale e del benessere generale, nonché gli aspetti del funzionamento sessuale, del livello di soddisfazione individuale della vita e ambientale. L'HRQoL è una misura della complessiva QoL (*Quality of Life*) [6] ed è molto importante nelle malattie progressive croniche nel quale il trattamento non può curare la malattia ma può portare dei vantaggi secondari che possono aumentare il livello soggettivo di soddisfacimento dei propri bisogni, indipendentemente dallo stato di salute fisico o dalle condizioni socioeconomiche.
Un deterioramento dell'HRQoL si ha durante le ricadute tipiche nella SM. Anche gli aspetti fisici dell'HRQoL si deteriorano con l'aumento della disabilità producendo consistenti risultati sulla totale HRQoL e sugli aspetti psicosociali. Recenti risultati di studi sul costo della malattia, eseguiti in Germania, Olanda e Inghilterra suggeriscono che HRQoL decresce in associazione con un progressivo livello alto di EDSS: un punteggio EDSS > 7,0 dello stato

di salute era valutato come "peggio di essere morto" da molti pazienti di questo gruppo [7].
Le disfunzioni cognitive influenzano il 43-59% dei pazienti, avendo un ripercussione negativa sulla qualità della vita. I pazienti con SM che hanno un indebolimento cognitivo dimostrano di essere meno attivi professionalmente, più dipendenti, meno occupati socialmente e riportano una maggiore alterazione sessuale rispetto ai pazienti senza problemi cognitivi, inoltre, i gravi problemi di fatica e emozionali, molto frequenti nei pazienti SM, hanno un ulteriore impatto sulla loro qualità della vita. La fatica infatti, è uno dei più comuni sintomi della disabilità che vivono le persone con SM. Oltre l'87% delle persone con SM riferiscono di avere, come principale problema "la fatica", descrivendola come un opprimente senso di stanchezza o spossatezza [8]. Le cause del "senso di fatica" sono sconosciute, non sembrano essere in relazione con l'età, il genere, la gravità, la durata della malattia o il tipo di SM. Molti ricercatori credono che ci sia una base biologica e che essa possa essere considerata uno specifico sintomo della SM. Viene anche descritta, a partire da una prospettiva psicologica, come uno stato di peggioramento che è in relazione alla riduzione della motivazione. Più specificatamente, gli individui che non sono motivati nello svolgimento delle loro attività, tendono a sentire più fatica [9]. La fatica è difficile da definire perché è una sensazione soggettiva che causa il dolore, quindi difficile da quantificare senza ricorrere all'autovalutazione.
Analogamente, se si accetta che la percezione dei pazienti della QoL è importante e che le misure di autovalutazione forniscono affidabili e valide informazioni, allora, un questionario di autovalutazione sulla QoL basato sulle esperienze dei pazienti e visione da parte di loro stessi, può dare ulteriore valore alla valutazione nei pazienti con SM. La misura della qualità della vita aiuta a fornire una più ampia quantificazione dell'impatto della malattia e a sviluppare un programma di cura da adattare ai bisogni del paziente [10].

Obiettivi

L'obiettivo della seguente ricerca è la valutazione della qualità della vita nei pazienti con SM, data l'imprevedibilità dei sintomi, con un incerto ritmo di progressione e un'incapacità di controllo e cura degli stessi. Uno dei principali traguardi è di ottimizzare la qualità della vita.
Essa è stata definita come "soddisfazione soggettiva della vita" [11]. È necessario individuare l'impatto multidimensionale di malattie come la SM, attraverso l'analisi del funzionamento fisico, sociale e del benessere emotivo.
Da alcune ricerche [12] è emerso come una più povera qualità della vita sia in relazione all'aumento dell'interferenza della SM nelle attività sociali. Si è anche trovato che i pazienti con SM sono significativamente meno soddisfatti della loro vita delle altre popolazioni di malati. Aronson [13] suggerisce che impedire l'interferenza della SM sulle attività sociali può essere un fattore chiave nel miglioramento della qualità della vita e previene l'istituzionalizzazione.
Si è voluto prendere in considerazione il sintomo "senso di fatica" a causa della sua particolarità sia nell'esordio (brusco e improvviso), nella manifestazione, tale da rendere il soggetto totalmente invalidante, che nell'incidenza (vengono colpiti tutti i soggetti SM), per vedere quanto influisce sulla qualità della vita.

Materiali e metodi

Il campione

Sono stati testati 32 pazienti con una diagnosi confermata di SM, in un periodo di tempo che va da febbraio ad aprile 2003, i soggetti sono stati reclutati presso l'Unità Operativa di Medicina Riabilitativa dell'Azienda Ospedaliera di Parma e del centro AISM della medesima città.
I criteri di inclusione in base ai quali i pazienti entrano a far parte del campione, sono:

- afferire al centro riabilitativo nel periodo che va da febbraio ad aprile (per le visite fisiatriche periodiche o per la fisioterapia);
- avere una EDSS < 7 (a causa dell'impossibilità di misurare la variabile "fatica" attraverso la scala MFIS);
- aver dato il consenso alla ricerca.

Le caratteristiche del campione, costituito da un totale di 32 soggetti, sono descritte in dettaglio nella Tabella I. Mentre nella Figura 1 si rappresenta la frequenza dei soggetti con forme diverse di SM.

Materiale

Tutti i soggetti sono stati sottoposti a due test:

- *Multiple Sclerosis Quality of Life* (MSQoL-54) per la valutazione della qualità della vita. È uno specifico strumento di misura dell'HRQoL nei pazienti con SM, costruito originariamente per soggetti di lingua inglese. Il test consiste di 54 item: di cui 36 provenienti dalla SF-36, precedentemente adattata alla popolazione italiana, e 18 item aggiuntivi che esplorano i campi relativi ai pazienti con SM (modulo MS-18).
  Gli Autori [14], hanno tradotto e adattato alla cultura italiana il modulo MS-18 dell'MSQoL-54, e validato clinicamente l'intero questionario. È stato valutato il contributo della disabilità sul punteggio del MSQoL-54 e la media ottenuta è stata comparata con i dati normativi della popolazione generale italiana e con l'originale campione di pazienti con SM degli Stati Uniti [15].
  La scala MSQoL-54 è costituita da due parti: salute fisica e salute mentale. Ognuna è suddivisa in sottoscale (Tab. II), ciascuna delle quali è valutata attraver-

TABELLA I.
Caratteristiche del campione normativo. *Characteristics normative sample.*

		Media	Deviazione standard	Range	Percentuale	Frequenza
Età		41,69	11,69	63-41,7		
Sesso	F				65,6%	21
	M				34,4%	11
Tempo dalla diagnosi		6,59	4,38	1-20		
Tempo dall'esordio		10,13	7,33	1-30		
EDSS		3,58	1,71	1-6,50		
Tipo SM	RR				28,1%	9
	SP				34,4%	11
	PP				3,1%	1
	PR				34,4%	11

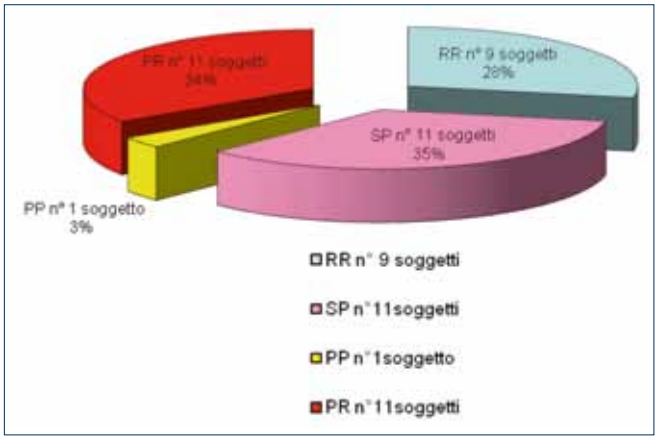

FIGURA 1.
Frequenza delle quattro forme di SM nel campione studiato. *Attendance the four form MS in normative sample.*

so più domande del questionario. Le domande sono per la maggior parte con risposte su scala Likert (a 3, 5 e 7 punti), altre prevedono risposte dicotomiche e una è su scala analogica a 10 punti. Tutti i punteggi vengono trasformati in scala da 0-100 e poi sommati all'interno di ogni sottoscala per ottenere il subtotale. Dividendo il subtotale per il numero delle risposte, si ottiene il punteggio finale della sottoscala. I punteggi finali vengono a loro volta moltiplicati per un numero specifico ad ogni sottoscala; sommando i punteggi così trasformati si ha un valore per la "salute fisica" e uno per la "salute mentale". Questi due valori, sommati, danno il punteggio finale della MSQoL-54. I punteggi più alti dimostrano una migliore HRQoL nei pazienti [16].

Questa scala ha il vantaggio di avere sia una valutazione generica sia specifica della qualità della vita nei pazienti con SM [17]. Si è dimostrato avere un'alta attendibilità test-retest (coefficienti di correlazione intraclass, 0,66-0,96) e un'alta consistenza interna (0,75-0,96) con evidente sostegno nel contenuto e nella validità di costrutto.

- *Modified Fatigue Impact Scale* (MFIS), include 21 domande. L'MFIS è una modificazione della *Fatigue Impact Scale* (FIS) [18], basata su item derivati da interviste con pazienti con SM che descrivono come la fatica influisce sulla loro vita. È un questionario di auto-valutazione che i pazienti possono generalmente completare con pochi o nessun intervento da parte dell'intervistatore. Il tempo di somministrazione è, approssimativamente, di 5-10 minuti.
  Il punteggio totale della scala MFIS può variare da 0 a 84 e viene calcolato sommando le tre sottoscale: *fisica*, il cui punteggio può raggiungere un valore da 0 a 36 e si completa sommando i punteggi di nove dei 21 item che costituiscono la scala; *cognitiva*, che può raggiungere un punteggio da 0 a 40 sommando i punteggi di 10 domande; *psicosociale*, il cui punteggio può andare da 0 a 8 sommando 2 item della scala. Tutte le domande sono con risposte su scala Likert a 5 punti (da 0 = mai a 4 = quasi sempre).
  L'MFIS è facile da somministrare e si concentra sul modo in cui la fatica nella SM, influenza la vita quotidiana, le abilità di auto-cura come la cura personale [19]. Essa infatti, influenza non solo i sintomi somatici come la debolezza muscolare, il capogiro, la mancanza di equilibrio, ma anche i sintomi cognitivi come la difficoltà di memoria, attenzione e concentrazione [20].

TABELLA II.
Il Test MSQoL-54: la sottoscala Salute Fisica e Salute Mentale. *The Test MSQoL-54: the understairs Physical Healthy and Mental Healthy.*

Scala della Salute Fisica	Scala della Salute Mentale
Funzione fisica	Preoccupazione per la salute
Percezione della salute	Generale qualità della vita
Energia/Fatica	Benessere emotivo
Ruolo limitazione fisica	Ruolo limitazione emotiva
Dolore	Funzione cognitiva
Funzione sessuale	
Funzione sociale	
Preoccupazione per la salute	

Procedure di somministrazione

Tutti i soggetti sono stati sottoposti al test MSQoL-54 dopo essere stati informati degli scopi della ricerca e aver dato il loro consenso.
La somministrazione è avvenuta al termine delle visite fisiatriche o dei cicli di fisioterapia a cui periodicamente si sottoponevano, presso l'Unità Operativa di Medicina Riabilitativa dell'Azienda Ospedaliera e/o dell'AISM di Parma.
Mentre il test MFIS, essendo uno strumento utilizzato dai fisiatri per ottenere una misura di autovalutazione della fatica, veniva somministrato ai pazienti durante le visite.
Analisi dei dati
Sono stati calcolati i valori medi per le diverse fasce di età in cui è stato suddiviso il campione: cinque gruppi, da 1 a 20, da 21 a 30, da 31 a 40, da 41 a 50 e da 51 a 60, in relazione alla qualità della vita.
È stato utilizzato il test Mann-Whitney, dopo aver suddiviso il campione, in maschi e femmine, in relazione alla variabile salute fisica e salute mentale della MSQoL-54, per verificare l'esistenza di differenze nella QoL tra le due popolazioni di soggetti.
Lo stesso test è stato usato, suddividendo il campione in quattro gruppi in relazione al tempo trascorso dalla data della diagnosi all'anno corrente, per valutare l'eventuale influenza della durata della malattia sulla QoL dei pazienti con SM.
È stata calcolata la correlazione tra i punteggi totali delle due scale della MSQoL-54, che misurano la salute fisica e mentale, e la MFIS, attraverso il test Rho di Spearman, per valutare l'esistenza di relazioni che permettono di individuare un possibile legame tra le due variabili. A queste sono state aggiunte ulteriori correlazioni tra le sottoscale della scala salute fisica e mentale (Tab. II) e il punteggio totale della scala MFIS, per individuare quali delle funzioni misurate della sottoscale sono correlate con la variabile che misura la fatica.
Anche le altre variabili: EDSS e il tempo dall'esordio (gli anni trascorsi dai primi sintomi all'anno corrente), sono state correlate con i due punteggi della scala fisica e mentale della MSQoL-54, per vedere l'esistenza di una qualche relazione fra essi.

Risultati

Il campione si dimostra eterogeneo, in quanto, suddividendolo in cinque gruppi di fasce di età differenti: da 1 a 20 (numero di soggetti: 4), da 21 a 30 (numero di soggetti: 14), da 31 a 40 (numero di soggetti: 4), da 41 a 50 (numero di soggetti: 6), da 51 a 60 (numero di soggetti 4) e valutando il valore medio per le diverse fasce di età, in relazione alla qualità della vita, (il primo gruppo ha una media di 60,27 per la scala che misura la salute fisica e di 65,14 per la salute mentale; il secondo gruppo ha media 60,08 per la salute fisica e di 75,24 per la salute mentale; il terzo gruppo ha media di 54,22 per la salute fisica e di 71,99 per la salute mentale; il quarto gruppo ha media 55,79 per la salute fisica e di 81,03 per la salute mentale; e in fine l'ultimo gruppo per la scala che misura la salute fisica ha una media di 45,51 e per la salute mentale 65,78) sono risultati esserci due valori, relativi alle fasce di età da 41a 50 e da 51a 60, che si discostano dalle tendenze centrali, indicativo di un campione che non si distribuisce normalmente (Fig. 2).
Applicando il test di Spearman Rho, non sono emerse correlazioni significative tra l'età e i punteggi totali delle due scale, fisica e mentale, che costituiscono la MSQoL-54.
L'unica correlazione che questa variabile sembra avere è negativa con due delle sottoscale che misurano la salute fisica: funzione fisica (rho = -,443; $p < ,05$) e funzione sessuale (rho = -,432; $p < ,05$).
L'EDSS non sembra essere correlato con le scale MSQoL-54 e con la scala MFIS, tranne per la sottoscala sulla funzione fisica con cui è correlato negativamente

(rho = -,599; p < ,05), mentre ha una correlazione positiva con il tempo trascorso dalla diagnosi, prendendo come punto di riferimento l'anno 2003 (rho = -,360; p < ,05).
Il tempo trascorso dall'esordio è positivamente correlato con la funzione cognitiva (rho = ,448; p < ,05), mentre è negativamente correlato con la funzione fisica (rho = -,420; p < ,05).
È emersa una correlazione negativa tra il punteggio totale della scala che misura la salute fisica e la scala MFIS (rho = -,523; p < ,01) e una ulteriore correlazione negativa tra la scala di misura della salute mentale e la scala MFIS (rho = -,530; p < ,01).
Tra le sottoscale della salute fisica, della MSQoL-54, quelle correlate negativamente con il punteggio totale MFIS sono: quelle che misurano la percezione della salute (rho = -,424; p < ,05), l'energia/fatica (rho = -,407; p < ,05), le limitazioni nel ruolo fisico (rho = -,430; p < ,05), le funzioni sessuali (rho = -,512; p < ,01), le funzioni sociali (rho = -,392; p < ,05).
Mentre le sottoscale che misura la salute mentale, della MSQoL-54, correlano negativamente con il punteggio totale MFIS, sono: la generale qualità della vita (rho = -,536; p < ,01), il benessere emotivo (rho = -,365; p < ,05), la limitazione nel ruolo emotivo (rho = -,406; p < ,05).
Prendendo in considerazione gli anni trascorsi dalla diagnosi al 2003 e la misura della qualità della vita, è stato suddiviso il campione in quattro gruppi: il primo va da 1 a 5 anni (n° di soggetti: 16), da 6 a 10 anni (n° soggetti: 11), da 11 a 15 anni (n° soggetti: 3) e da 16 a 20 anni (n° soggetti: 2).

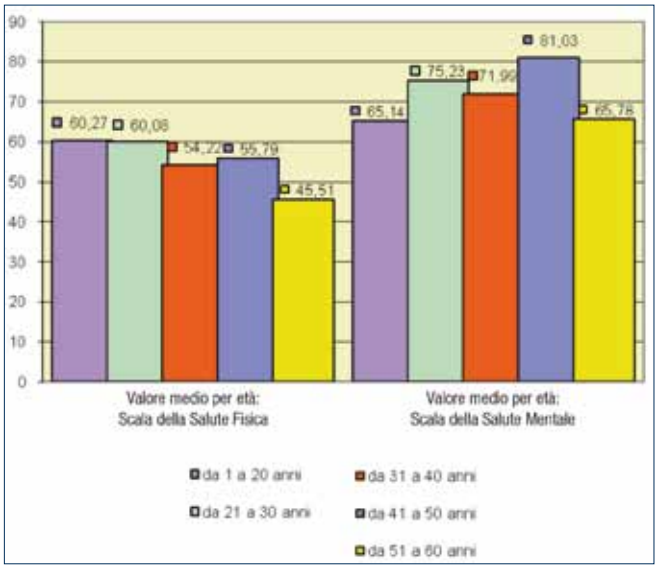

FIGURA 2.
Distribuzione del campione. *The distribution normative sample.*

Sono emerse delle differenze statisticamente significative (U = 37,000; p < ,05) nella qualità della vita in particolare rispetto alla scala che misura la salute fisica, tra i soggetti con un tempo trascorso dalla diagnosi da 1 a 5, rispetto ai soggetti con una diagnosi dai 6 ai 10 anni. Un'altra differenza statisticamente significativa è emersa tra questi ultimi e i soggetti la cui diagnosi va dagli 11 ai 15 anni fa nella scala che misura la salute fisica (U = ,000; p < ,05). Rispetto alle altre fasce di gruppi non sono emerse differenze significative.

Conclusioni

Le correlazioni negative emerse tra i punteggi totali della MSQoL-54 e il totale MFIS, (rho = -,523, p < ,001; rho = -,530, p < ,001), potrebbero indicare che a una maggiore alterazione del senso di fatica, corrisponda una diminuzione della QoL, inclusa sia la componente fisica che mentale.
La fatica sembra essere maggiormente in relazione con alcune variabili della salute fisica, indicando che a un peggioramento nel senso di fatica corrisponde un deterioramento nelle funzioni legate alla salute fisica, tra cui ricordiamo la percezione che il soggetto ha della sua salute, il livello di energia e fatica, il ruolo delle limitazioni fisiche e il funzionamento sessuale e sociale.
Un ulteriore declino delle funzioni nel soggetto, a seguito dell'aumento del senso di fatica, può essere individuato nelle funzioni mentali [21], in particolare nella generale qualità della vita, nel benessere emotivo e nel ruolo delle limitazioni emotive.
L'indagine ha l'obiettivo di scoprire se la QoL possa essere condizionata da altre variabili come l'EDSS, utile indicatore della misura globale del livello di disabilità nel paziente, che sembra però, non avere nessuna relazione né con la fatica né con la qualità della vita, tranne, per quest'ultima, con il funzionamento fisico, per cui un punteggio elevato nella EDSS potrebbe coincidere con un'alterazione in queste funzioni mentre, ha una relazione positiva con il benessere emotivo e le funzioni cognitive potendo così indicare che a un punteggio elevato, nella EDSS, coincide un aumento in queste due funzioni. Seppure, in altri studi è emerso che un aumento del valore della EDSS era associato con la disabilità in molte scale della salute fisica e mentale ma, era meno correlato con le alterazioni sessuali e cognitive [22].
Per quanto riguarda l'età dei soggetti con SM sembra che, all'aumentare dell'età diminuiscano le funzioni fisiche e sessuali, ma non sembra esserci una qualche differenza nelle altre funzioni misurate.
Infatti, più che l'età dei soggetti con SM, sembra maggiormente influente, sulla qualità della vita, la durata della malattia, calcolata nel numero di anni trascorsi tra l'anno della diagnosi e l'anno corrente 2003. Le differenze sem-

brano indicare che, tra chi ha una durata della malattia dai 6 ai 10 anni e i soggetti la cui diagnosi dura dagli 11 ai 15 anni, c'è una differenza della QoL in particolar modo per la salute fisica; mentre la differenza della QoL, emersa tra i soggetti la cui diagnosi è stata fatta da 1 a 5 anni fa rispetto ai soggetti con un tempo dalla diagnosi dai 6 ai 10 anni, è specifica per la salute mentale.
Anche gli anni trascorsi dall'esordio della malattia si dimostrano essere in relazione con alcuni aspetti della QoL, in particolare con la funzione cognitiva che sembra aumentare insieme al numero di anni dalla diagnosi, mentre diminuiscono le funzioni fisiche.
Per quanto riguarda la differenza nel tipo di SM diagnosticata sui pazienti, non sembrano esserci differenze statisticamente significative, ciò potrebbe indicare che non è questo fattore a incidere sulla vita del soggetto. Bisogna comunque tener presente i risultati di altri studi che sembrano dimostrare, invece, che i pazienti con diagnosi di SM di tipo SP, hanno avuto un punteggio più basso nella QoL rispetto ai pazienti con SM di tipo RR e che la disabilità neurologica è in relazione con la disabilità della qualità della vita [23].
Il cambiamento del comportamento, nelle persone con SM è stato osservato sia dai pazienti che dai familiari, questi cambiamenti influiscono sulla QoL in riferimento alla salute mentale, al funzionamento fisico e sociale [24].
Alla luce dei risultati ottenuti, sembra doveroso sottolineare l'importanza della valutazione che i pazienti con SM danno della propria salute e dell'effetto aggiuntivo che variabili esterne e spesso non direttamente legate alla malattia, come i pregiudizi, gli stereotipi nei confronti di questi soggetti (come in altre malattie croniche), le barriere architettoniche ecc., hanno sulla condizione del singolo.
L'introduzione di una misura della QoL durante la valutazione dei risultati dei trattamenti medici specifici potrebbe risultare utile indicatore per stimare gli effetti del trattamento ottenuti e a partire dalla misura della QoL individuare i rischi di un possibile aggravamento dello stato di salute del soggetto a causa di un deterioramento nelle funzioni sia fisiche che mentali alla base di molte alterazioni psicologiche come, la perdita di identità, disistima, senso di impotenza, mancanza d'indipendenza, perdita di controllo personale, paura del futuro, che spesso conduce a gravi depressioni.
L'auto-efficacia si riferisce alla convinzione individuale della propria abilità, nel vincere specifiche sfide e include la conoscenza profonda, l'auto-stima e la sensazione di essere capaci di controllare gli eventi presenti e futuri. L'auto-efficacia nella SM è stata dimostrata capace di predire il 24% degli adattamenti alla malattia influenzando l'auto-stima e l'auto-valore.
L'esistenza della depressione al fianco della SM può incrementare la sofferenza nella vita del paziente, ostacolando la riabilitazione, riducendo la motivazione, suggerendo che la combinazione tra SM e depressione, può determinare un aumento del rischio di suicidio. Come anche l'ansietà può influenzare l'indebolimento fisico durante le attività quotidiane.
Questi dati sono stati sostenuti da studi i cui risultati dimostrano una correlazione significativa tra i disturbi dell'umore, problemi cognitivi e la fatica.
Molte persone disabili guadagnano un'alta QoL attraverso modificazioni ambientali o attraverso un aumento apprezzabile delle abilità funzionali che essi possiedono, questo li porta a non considerare la loro vita come caratterizzata da una bassa salute relativa alla QoL.
Un certo numero di fattori può influenzare l'impatto e l'adattamento alle malattie croniche, in modo da non incidere particolarmente sulla QoL, questi includono: la personalità dei pazienti, l'esperienza precedente con eventi simili, la natura progressiva della malattia, il livello di sostegno realmente ricevuto e la percezione che hanno delle strategie di adattamento ritenute adeguate a ottenere una modificazione dei risultati.
Si potrebbe confermare l'ipotesi circa l'impatto che la SM ha sulla QoL dei soggetti che hanno ricevuto la diagnosi in quanto responsabile dell'alterazione di alcune funzioni, più di altre, legate sia allo stato di salute fisica che allo stato di salute mentale e queste sembra si aggravino in concomitanza dello "stato di fatica", indipendentemente dal tipo di SM diagnosticata.
Da quanto è emerso precedentemente, lo "stato di fatica" è non solo molto comune ma incide profondamente sulla funzionalità e il benessere psico-fisico del soggetto. Infatti, sembra che a un aumento della compromissione della funzionalità fisica, cognitiva e psicosociale, valutata dalla MFIS corrisponde una minore QoL, sia dello stato di salute fisico che mentale.
Non sembra esserci nessuna relazione tra la QoL e il sesso dei soggetti, indicando con ciò che un'eventuale alterazione della QoL può manifestarsi tanto nelle donne che negli uomini.
Seppur considerevolmente significativi, questi risultati non possono essere generalizzati, data la distribuzione del campione eterogeneo che è stato reperito.
Ottenere una misura della QoL potrebbe anche non cambiare il decorso della patologia in sé, essendo determinata da alterazioni principalmente di natura biologica ma, il cambiamento nel concetto di salute, definito dall'OMS come uno stato di completo benessere, mentale e sociale e non semplicemente come assenza di malattia, impone di non trascurare la considerazione del concetto di malattia come risultato di un'interazione di fattori sociali, psicologici e biologici.
Ciò implica la necessità di non dover più guardare alla sola malattia, andare alla ricerca delle cause possibili, dei trattamenti medici più adatti per il caso specifico, come da sempre il modello biomedico tradizionale ha fatto.

Bisogna concepire la patologia come una condizione del soggetto, che altera non solo il suo equilibrio psicofisico ma anche il suo contesto sociale, relazionale, le aspettative e gli obiettivi futuri, la motivazione a perseguirli, con il rischio di aggravare il suo stato di salute.
Questo è particolarmente vero per le malattie croniche come la SM, che oltre a essere imprevedibile e ad andamento altalenante, manifesta una poliedricità di sintomi che alterano considerevolmente la vita dei soggetti. Oltre alla debolezza, la paralisi, l'indebolimento visivo e della vescica, il dolore cronico e la fatica profonda, sono particolarmente frequenti i disordini dell'umore, specialmente la depressione e i disturbi d'ansia. Proprio per queste condizioni, la SM ha un enorme impatto su molti aspetti della vita del soggetto.

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Efficacy of supportive family interventions in bipolar disorder: a review of the literature

Efficacia degli interventi di sostegno familiare nel disturbo bipolare: una review della letteratura

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Summary

Background

To review the efficacy of supportive family interventions for bipolar disorder on patients' clinical and social outcome and family functioning.

Methods

A review of the studies on supportive family interventions in bipolar disorder carried out in the last 20 years has been performed using the main databases. Searched keywords include "psychoeducational family intervention", "family therapy", "family supportive interventions", "caregivers"; these terms have been matched with "bipolar disorder", "affective disorders" or with "manic-depressive illness".

Results

The different approaches developed, alone or integrated with more complex treatment strategies, can improve the course of bipolar disorder, reduce the risk of relapses and hospitalizations and improve patient adherence to pharmacological treatment. Only few studies have tested the efficacy of these interventions on the reduction of suicidal ideation or in patients with an early onset of the disease. Supportive family interventions improve coping strategies of relatives and family burden.

Conclusions

Supportive family interventions should be an integral part of optimal management of bipolar disorder. Studies on the implementation of these interventions in routine practice are needed.

Key words

Bipolar disorder • Supportive family intervention • Psychoeducation, family burden

Background

Bipolar disorder occurs in 1 to 3.7% of the general population and will represent the sixth leading cause of disability worldwide among all medical illnesses by the year 2020 [1-3]. The disorder has a significant impact on social functioning and quality of life of affected people and their relatives [4].

The illness is highly recurrent with 40-60% of patients experiencing at least one relapse of depression or mania within two years, even if they are on a regular pharmacological treatment [5]. Patients present multiple impairments in school, work and social functioning, even when they are asymptomatic [6-10]. Suicide risk is 15 times higher in bipolar patients compared to the general population [11 12] and mortality rates due to suicide rise up to 15-20% [13]; moreover, as many as 50% of patients attempt suicide at least once [14].

The family environment plays an important role in this disorder [15], similar to schizophrenia [16 17] and major depression [18]. In bipolar disorder, family burden is mainly associated with: a) manic symptoms; b) poor social functioning; c) presence of an acute episode during the last two years; d) rapid cycling course of illness; e) lack of adherence to pharmacological treatment [2 19 20].

A study carried out in 500 caregivers of patients with bipolar disorder has highlighted that 89% expressed concerns for the patient's behaviour, 52% for loss of social role and 61% for discontinuation of family daily life [21]. Caregivers with high levels of family burden report a high number of physical problems, depressive symptoms, high risky behaviours, frequent referral to health agencies and less support from the social network.

During the last 10 to 15 years several studies have shown that active involvement of family in the treatment of patients with bipolar disorder improves outcome by reducing family burden and improving communication skills [22]. Thus, family interventions have been proposed for an optimal management of bipolar patients [23].

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Family interventions, according to the available evidence, represent one of the most effective psychosocial interventions for the treatment of bipolar disorder [24]. Several models have been developed, all being "psychoeducational" in nature, meaning that patients and/or relatives are thought to manage and recognize affective episodes early. The "family-focused therapy" (FFT), developed by Miklowitz et al. in the early 2000s, consists of 21 psychoeducational sessions including a special training for the improvement of problem-solving strategies and communication skills. This approach specifically focuses on strategies to manage emotions and to improve interpersonal communication [23]. The model developed by Colom and Vieta [25] is delivered without the patients and aims to provide relatives with information about the nature of the illness and with coping strategies for its management. Lam et al. [26] have developed an educational intervention which combines information modules and cognitive skills to modify the behaviours of patients and relatives. The approach developed by Ian Falloon [27 28] for the management of schizophrenia has been adapted to bipolar disorder only recently by our group [29], and its results will be described elsewhere.

The aim of the present paper is to review the current status of research on the efficacy of supportive family interventions on clinical status and social functioning of patients with bipolar disorder and on outcomes in relatives.

Methods

All studies on supportive family interventions for bipolar disorder carried out over the last 20 years (until June 2012) have been searched through Medline/Pubmed databases. The keywords "psychoeducational family intervention", "family therapy", "family supportive interventions", "caregivers", "family burden" were used in the search and matched with "bipolar disorder", "bipolar affective disorder" and "manic-depressive illness". Only papers in English were considered for this review. In this paper, "supportive family intervention" and "psychoeducational family intervention" will be considered as synonymous, although we are aware that they are not.

The results have been grouped into three areas: 1) efficacy of supportive family interventions on patients' clinical status; 2) efficacy of supportive family interventions on relatives' outcome; 3) efficacy of supportive family interventions on early onset bipolar disorder. This review does have not to be considered a systematic review, but rather as a description of evidence-based data supporting the implementation of supportive family intervention for bipolar disorder in routine care, as has been done recently for psychosocial interventions for the same disorder [30].

Results

Efficacy of supportive family interventions on patients' outcomes

Several studies showed that this intervention improves the course of bipolar disorder, in particular by preventing relapses and reducing hospital admissions [31 32].

Miklowitz et al. [33 34] randomly assigned 101 adult patients and their relatives, in a post-manic, mixed or depressive episode to two alternative groups, one receiving a family-focused therapy (experimental group) and the other receiving two-sessions of a family intervention focused on crisis management (control group). Patients from both groups were on regular pharmacological treatment. At two years, experimental intervention had a high impact in reducing depressive symptoms, probably as a consequence of improvement in communication skills between patients and family members. Moreover, the experimental group showed a lower number of relapses (52% *vs*. 17%) and a longer period free from symptoms (73.5 weeks *vs*. 53.2 weeks).

Rea et al. [35] compared family-focused therapy with individual psychotherapy in 53 bipolar I patients admitted to a psychiatric ward for a manic episode. The individual psychotherapy was scheduled according to the educational topics of the family-focused treatment (21 sessions over a 9-month period). Although after one year no difference was found between the two groups, at two years patients in the family-focused group showed a relapse rate of 28% and an admission rate of 12% compared to a relapse rate of 60% and an admission rate of 60% in the control group.

Reinares et al. [36 37] carried out a study to analyze the effects of a psychoeducational programme for caregivers on the course of bipolar disorder. 113 outpatients living with caregivers were randomly assigned to an experimental or a control group; the former group received 90-min psychoeducational sessions providing information about the illness and the improvement of coping strategies. The sessions were run without the patients. Caregivers from the control group did not receive any kind of intervention. Patients were assessed monthly during the intervention and at 12 months after the end of the protocol. In the experimental group, a significant reduction of relapses and a longer period in remission have been observed.

Miller et al. [38] reported that the provision of any family treatment (family therapy or psycho-educational intervention) significantly improves the course of bipolar disorder, particularly the number of depressive episodes and the time spent in a depressive episode. A few studies have analyzed the impact of psychoeducational family intervention on suicide risk.

Several psychosocial approaches (i.e. cognitive behav-

TABLE I.
Efficacy of psychoeducational family interventions on patients' clinical status. *Efficacia degli interventi di sostegno familiare sullo stato clinico e il funzionamento sociale del paziente.*

Study, (Year), Country	Sample size (N)	Study design	Inclusion criteria	Main features of the interventions	Main results
Miklowitz et al., (2000; 2003), USA [33 34]	101 adults patients and their family members	Family-focused therapy (FFT) *vs*. crisis management (CM) Random allocation	1) Diagnosis of bipolar disorder in the past 3 months; 2) age between 18 and 65 years; 3) no neurological disorder, alcohol and substance abuse disorder within 6 months; 4) in regular contact or living at least 4 hours per week with a caregiver	FFT: 21 psychoeducational sessions on communication and problem-solving skills CM (crisis management): 2 one-hour, home-based family education sessions on relapse prevention and resolution of family conflicts	Effects were more evident on depressive symptoms than on manic ones During the two-years follow-up, FFT group showed a lower number of relapses and a longer relapses-free period FFT group showed a better pharmacological compliance and improvement in global functioning compared to the control group
Rea et al., (2003), USA [35]	53 patients and 74 relatives	Family-focused therapy (FFT) *vs*. individually focused patient treatment Random allocation	1) Diagnosis of bipolar I disorder; 2) admission in a psychiatric ward for a manic, mixed or depressive episode; 3) age between 18 and 65 years; 4) absence of neurological disorder, or substance abuse disorder during the last 6 months; 5) in regular in contact with the mental health centre (at least 4 hours per week with a caregiver)	21 psychoeducational sessions, on communication and on problem-solving skills	At 2 years, FFT group showed a lower relapse and admission rates than control group
Reinares et al., (2008; 2010), Spain [36 37]	113 caregivers of patients with bipolar I disorder	Caregivers' psychoeducational intervention *vs*. control group Random allocation	1) Diagnosis of bipolar I or II disorder; 2) age between 18 and 60 years; 3) absence of symptoms for at least three months; 4) on regular pharmacological treatment; 5) living with a relative for at least 1 year; 6) absence of comorbidity with other axis I disorders	Twelve 90-min psychoeducational sessions on information about the nature of the illness and on coping strategies	The experimental group showed a significant reduction of manic or hypomanic relapses and a longer period disease-free particularly during the early stages of the illness
Miller et al., (2008), USA [38]	92 patients with bipolar I disorder and their family members	Pharmacotherapy alone vs. family therapy + pharmacotherapy *vs*. multi-family psychoeducational group + pharmacotherapy Random allocation	1) Current mania, major depression, or mixed episode; 2) age between 18 and 75 years; 3) living with a relative	Family therapy was conducted according to the McMaster model of family functioning (a short-term, multidimensional treatment that emphasizes comprehensive assessment and problem-solving strategies)	In patients from families with high levels of impairment, the addition of the family intervention resulted in a significantly improved course of illness, particularly by reducing the number of depressive episodes and the proportion of time spent in a depressive episode

Clarkin et al., (1990; 1998), USA [43 44]	42 patients and their spouses randomly assigned to receive both medication and the psychoeducational marital intervention, and 23 patients to receive medications only	Psychoeducational interventions + pharmacotherapy *vs.* pharmacotherapy alone Random allocation	1) Age between 21 and 65 years; 2) diagnosis of major affective disorder or bipolar disorder; 3) married or living with a relative for at least six months; 4) absence of organic brain disorder, or of alcohol and drug abuse; 5) no pregnancy; 6) absence of contraindications to the use of lithium or carbamazepine	25 psychoeducational sessions: 10 sessions scheduled weekly, 15 bimonthly. The intervention lasts 11 months	At the end of the intervention, patients showed an improvement of compliance to pharmacological treatment and of social functioning

ioural therapy, family focused therapy, interpersonal and social rhythms therapy, systematic treatment enhancement programme for bipolar disorders) have shown a positive impact on the improvement of patient adherence to pharmacological treatments, a fundamental but rarely achieved therapeutic goal in the management of bipolar disorder [39-42]. Moreover, Clarkin et al. [43 44] reported that acute bipolar patients receiving an 11-months psychoeducational family intervention have a better adherence to treatments and global functioning than patients receiving pharmacological therapy alone. Miklowitz et al. [33 34] showed that family-focused therapy resulted in a better adherence to treatments at two years compared to those receiving management crisis intervention.

All studies on the impact of supportive family interventions on the clinical status of patients with bipolar disorder are reported in Table I.

Efficacy of supportive family interventions on relatives' outcomes

A few studies have analyzed the effects of psychoeducational family interventions on the well-being of relatives. Reinares et al. [45] randomly assigned 45 euthymic bipolar patients and their relatives to an experimental group receiving twelve 90-minute psychoeducational sessions on the clinical features of bipolar disorder and on the development of coping strategies or to a control group receiving pharmacological treatment alone. At the end of the intervention, treated caregivers reported lower levels of family burden. Eisner & Johnson [46] analyzed the effects of an intervention focused on the improvement of relatives' attitudes toward patients with bipolar disorder. Twenty-eight relatives received a 1-2 day multi-family intervention, and were assessed at baseline and after one week. At the end of the intervention, relatives had more information on bipolar disorder, but anger, criticism and attitudes toward the patients did not significantly change, thus confirming the difficulties in modifying the "expressed emotions" of relatives of patients with bipolar illness [46].

Perlick et al. [47] found a reduction of subjective burden in relatives receiving a family focused treatment-health promotion intervention. In the US, Ruffolo et al. [48] promoted a new brief psychoeducational approach, the so-called two-hours single-session family psychoeducation workshop. During the first hour, the clinician provides information on the illness to the relatives; in the second hour participating family members are divided into breakout groups for more intensive discussion and problem solving strategies. The results of this study confirm that this approach increases relatives' knowledge about the illness and improves their coping strategies. A similar result has been found by Jönsson et al. [49], who showed improved lifestyle behaviour and stress management in relatives re-

ceiving educational intervention. Madigan et al. [50] carried out a randomized controlled trial and grouped patients with bipolar disorder and their relatives in three arms, receiving multi-family group psychoeducation (MFGP), solution focused group therapy (SFGT) or treatment as usual (TAU). At one year, those who were allocated to either MFGP or SFGT showed significantly better knowledge about the disorder and reduced overall burden and psychological distress. These results were still significant at two years. The studies which have explored the impact of supportive family interventions on outcomes of relatives are reported in Table II.

Efficacy of supportive family interventions on early onset bipolar disorder

Childhood onset bipolar disorder is associated with significant morbidity and mortality, but effective treatment strategies are at the moment underdeveloped and understudied. In the US, 35 patients and their relatives were assigned to an experimental group receiving multi-family psychoeducation group (MFPG) intervention or to a control group in a waiting-list. At the end of the study, MFPG parents showed significantly greater knowledge about the illness compared to the control group [51]. Moreover, children from this group reported a significant improvement in social support from their parents and peers.
In the US, Goldstein et al. [52] assessed the feasibility of a dialectical behaviour intervention for young bipolar patients and found a reduction in suicidal thinking and depressive symptoms. Miklowitz et al. [53] explored the effects of parents' expressed emotion (EE) on the outcome of adolescent bipolar patients, and found that patients treated with family focused therapy had significantly improved depressive and manic symptoms compared to those receiving enhanced care. Studies allocated in this category are detailed in Table III.

Summary of findings and conclusions

Although a few randomized clinical trials have been carried out to evaluate the efficacy of supportive family interventions in bipolar disorder, this review is the first to analyze the benefits and limitations of supportive family interventions on patients' and relatives' outcomes.
The available data and guidelines [54] suggest combining pharmacological treatment with psychoeducational family intervention to achieve a comprehensive, good long-term outcome. In particular, this association reduces relapses and hospital admissions, improves social functioning and increases compliance to pharmacological treatment [24 55 56]. However, all studies have some important methodological limitations, such as small sample sizes, lack of randomization and short follow-ups [57], which do not allow the generalizability of available findings. Moreover, most of the studies did not take into account the various clinical subtypes of bipolar disorder and have not explored if the effects of this intervention vary according to the subtype. We anticipate that psychoeducational family intervention is more effective in bipolar I disorder than in the other spectrum subtypes, but this needs further investigation.
Although studies exploring the effect of psychosocial interventions on the reduction of suicidal risk are not available [58], new data are emerging on the effectiveness of these interventions in suicidal patients, but still suffer from methodological limitations. Although the association of family support with pharmacological treatment represents the optimal therapeutic strategy in patients with suicide risk, only a few studies have investigated the efficacy of psychoeducational interventions on the management of suicide ideation and attempts [59].
One of the most consistent findings among the different studies is that family psychoeducational interventions reduce subjective burden on relatives, improve coping strategies and increase knowledge about bipolar disorder and early warning signs [45 60]. This approach must be considered an essential component of the optimal treatment strategy of patients with bipolar disorder living with their relatives, since an improvement in the family environment significantly improves patients' outcome. On the other hand, it must be acknowledged that psychoeducational family intervention does not reduce the expressed emotions of relatives in bipolar disorder [45], although this construct has been explored in only one study and further research is needed.
Almost all studies have been carried out in experimental settings, and the difficulties, limitations and benefits in providing this intervention in routine care have not been explored. Only recently, our research group has performed a study to explore the difficulties in implementing psychoeducational family intervention according to the Falloon model in Italian routine care [28]. This study was carried out in 11 randomly selected mental health centres and found that organizational difficulties represent the main barrier to the dissemination of this intervention in clinical practice, which must be addressed at a decision-making level.
In conclusion, supportive family interventions are effective on several domains of bipolar disorder, in particular on relapses, treatment compliance and coping strategies of relatives. The efficacy of these interventions in patients with an early onset of the disorder is also documented, but requires further confirmation.
Further studies should be carried out to: a) explore the differences among the different proposed psychoeducational models; b) evaluate the effects of interventions in

TABLE II.
Efficacy of supportive family interventions on relatives' outcomes. *Efficacia degli interventi di sostegno familiare su benessere, funzionamento e opinioni dei familiari.*

Study, (Year), Country	Sample size (N)	Study design	Inclusion criteria	Main features of the interventions	Main results
Reinares et al., (2004), Spain [45]	45 euthimic bipolar patients and their relatives	Psychoeducational intervention for caregivers *vs*. standard pharmacological treatment Random allocation	1) Diagnosis of bipolar I or II disorder; 2) age between 18 and 60 years; 3) absence of symptoms for at least 3 months	Twelve 90-min psychoeducational sessions on information about the nature of the illness and on coping strategies	Caregivers improved their knowledge about the illness and showed a reduction of their subjective burden
Eisner & Johnson, (2008), USA [46]	28 relatives	Psychoeducational family intervention focused on emotions and on marital communication	1) Age between 18 and 70 years; 2) living with a patient with bipolar disorder	1 or 2 days multi-family group workshop	Relatives had more information on bipolar disorder, but no change in EE levels
Perlick et al., (2010), USA [47]	46 relatives	Family-focused treatment-health promoting intervention (FFT-HPI) *vs*. health education (HE) intervention Random allocation	1) Age ≥ 18 years; 2) living with a patient affected by bipolar disorder	FFT-HPI: 12–15 sessions of a family-focused, cognitive-behavioral approach HE: 8-12 health education sessions delivered via videotapes	The FFT-HPI group experienced a significant reduction in caregivers' depressive symptoms and in subjective burden. Psychoeducation and focused cognitive work with caregivers had an impact on patients' symptoms, even if the patient was not directly involved in the intervention
Ruffolo et al., (2011), USA [48]	353 participants (patients, parents, partner o close friends)	Single-session of family workshops	All patients and their caregivers in charge to the local mental health centre	Two-hours, single-session family psychoeducational workshops. During the first hour, information on the illness are provided. During the second hour, a more intensive discussion is performed in breakout groups	Patients and their relatives showed an increased knowledge and improved coping strategies
Jönsson et al., (2011), Sweden [49]	34 family members	Educational intervention	1) To be a relative of a patient with bipolar disorder; 2) patient is in charge in the outpatient mental health centre	10-sessions of an educational intervention designed for families of patients in charge in the mental health centre	The educational intervention improved relatives' understanding of the illness. A significant improvement in stress management and social functioning was obtained over time
Madigan et al., (2012), Ireland [50]	47 carers of 34 patients	Multifamily group psychoeducation (MFGP) *vs*. solution focused group therapy (SFGT) *vs*. treatment as usual (TAU) Random allocation	1) Age ≥ 18 years; 2) IQ > 80	MFGP: Five sessions of two hours scheduled weekly, performed by a psychiatric nurse and a psychiatric social worker SFGT: five sessions each lasting a 5-week period, carried out by two psychiatric nurses	At one and two years follow-up, in the MFGP and in the SFGT group a significant improvement of relatives' knowledge, reduction of family burden and of psychological distress was found

TABLE III.
Efficacy of supportive family interventions on early onset patients' outcomes. *Efficacia degli interventi di sostegno familiare nei pazienti ad esordio precoce.*

Study, (Year), Country	Sample size (N)	Study design	Inclusion criteria	Main features of the interventions	Main results
Fristad et al., (2002), USA [51]	35 patients and their parents	Multi-family psychoeducational group (MFPG) or waiting list Random allocation	Children aged from 8 to 11 years with a mood disorder	8 sessions on children illness and treatment options, training in communication exercises, and problem-solving strategies. During each session, caregivers and children meet separately, although their session content is thematically linked	MFPG parents showed significant improvement of knowledge about illness. The results were maintained at 6 months. MFPG children reported a significant improvement in social support from their parents
Goldstein et al., (2007), USA [52]	10 participants	Dialectical behavior therapy intervention	1) Age between 12 and 18 years; 2) diagnosis of bipolar I or II disorder with an acute manic, mixed, or depressive episode in the previous 3 months; 3) on a regular pharmacological regimen; 4) in contact with at least one relatives; 5) no mental retardation	24 alternative weekly sessions of family skills training or individual therapy	It had been reported an high attendance to the intervention protocol. The participants reported a reduction of patients' suicidal thinking and improvement of patients' non-suicidal self-harm behaviors, emotional dysregulation and depressive symptoms
Miklowitz et al., (2009), Spain [53]	58 adolescents with bipolar I or II disorder and 58 key-relatives	Family-focused therapy for adolescents (FFT-A) *vs*. enhanced care (EC) Random allocation	1) Age between 12 and 17 years; 2) diagnosis of bipolar I or II disorder; 3) a period of significant manic, mixed, hypomanic or depressive symptoms in the previous 3 months; 4) no evidence of mental retardation; 5) no substance abuse in the previous 3 months; 6) at least one participating parent	FFT-A: 21 sessions (12 weekly, 6 biweekly, and 3 monthly) EC: 3 weekly psychoeducational sessions with parents focused on relapse prevention, medication adherence, and communication skills	In the experimental group, adolescents living in high-EE families showed greater reductions in depressive and manic symptoms

long-term outcomes of the disorder; c) clarify the role of intervention on different clinical domains of the bipolar spectrum disorders.

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A review of self-report and interview-based instruments to assess mania and hypomania symptoms

Una rassegna degli strumenti autovalutativi ed eterovalutativi per valutare i sintomi maniacali e ipomaniacali

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Summary

Objective

The aim of this paper is to provide an overview of the self-report and interview-based instruments to assess mania/hypomania symptoms and related features, with a focus on 7 selected instruments in widespread use to illustrate their psychometric properties, comparative performance and pros and cons.

Methods

A systematic search strategy was devised and queried on Medline from 1973 to 2012 using the terms mania, hypomania, instrument, scale, questionnaire, interview, validity, reliability, psychometric properties and adults, elderly, aged. To be included, a study had to be published in a peer-reviewed journal or book in English or Italian.

Results

Of the 17 self-report instruments identified, two (the Mood Disorder Questionnaire (MDQ) and the Hypomania Checklist-32 (HCL-32), received the most research attention. Although the psychometric properties of these instruments are good, their use as screening instruments to detect hypomania in the community or in patients with depression is partially limited by their low positive predictive value, related to the low prevalence of this condition. Nonetheless, they can be efficiently used to rule out the presence of hypomania. The Altman Self-Rating Mania Scale is increasingly being used to monitor mania symptoms over time by phone or email in patients diagnosed with bipolar disorder because it consists of only 5 items. When the aim is early detection of manic/hypomanic symptoms that a patient may have experienced during their lifetime, the 33-item subset of the MOODS-SR seems promising because it includes the key psychopathology dimensions that better discriminate bipolar from unipolar disorder.

Of the interview-based instruments, the Young Mania Rating Scale and the Bech-Rafaelsen Mania Scale are the most widely used outcome measures in clinical trials. Although they were developed more than 30 years ago, they continue to be the gold standard for research purposes. The two instruments have a similar coverage, although the YMRS is preferred over the BRMAS because it includes an item on insight.

Conclusions

Although no instrument can replace the need for accurate clinical diagnosis based on patient history, we argue that the increasing use of self-report instruments to screen bipolar disorder in patients presenting with depression or to monitor mania/hypomania symptoms over time may contribute to increasing the use of routine standardized assessment. Measurement-based care as the standard of care has the potential to transform psychiatric practice, move psychiatry into the mainstream of medicine, and ultimately improve the quality of care for patients with psychiatric illness.

Key words

Mania • Hypomania • Bipolar spectrum • Rating scales • Interview • Questionnaire • Validity • Reliability

Introduction

Bipolar disorder is a serious illness associated with significant psychosocial morbidity and excess mortality. Recent research carried out by World Health Organization World Mental Health Survey Initiative in community adults from 11 countries worldwide indicated that bipolar disorder, when defined to include milder variants such as bipolar II disorder and subthreshold bipolar disorder, has a lifetime prevalence of 2.4% [1]. Studies carried out in psychiatric and primary care settings have found that bipolar disorder is sometimes under-recognized, particularly in patients presenting for treatment of depression [2-5]. Even for those patients diagnosed with bipolar disorder, the time lag between initial treatment seeking and correct diagnosis often exceeds 10 years [6 7].

The treatment and clinical implications of the failure to recognize bipolar disorder in depressed patients include the under-prescription of mood stabilizers, an increased

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risk of rapid, cycling and increased costs of care [7-10]. When symptomatic, patients with bipolar disorder are much more likely to experience symptoms of depression and anxiety rather than symptoms of mania or hypomania [11]. It is therefore frequent that, when presenting for treatment, patients with bipolar disorder are not in the manic or hypomanic phases of the illness. This suggests that manic phases, especially when brief or not characterized by impulse dyscontrol, need to be elicited with retrospective assessment, considering the frequent lack of subjective suffering, enhanced productivity, ego-syntonicity and diurnal or seasonal rhythmicity associated with several manic/hypomanic symptoms [12].

Recommendations for improving the detection of bipolar disorder include careful clinical evaluations inquiring about a history of mania and hypomania and the use of screening questionnaires [13-16]. A systematic classification of self-report and interview-based instruments to assess mania and hypomania might help the clinician to make the most appropriate instrument selection for the different research and clinical purposes [17].

In 2009, Picardi [18] reviewed the rating scales for bipolar disorder, according to the type of symptoms to be assessed (depressive, manic, psychotic) and the purpose of the instrument (screening, early identification). The aim of this paper is to provide a broader overview of the existing self-report questionnaires and of interview-based clinical instruments to assess mania symptoms and related features, with a focus on 7 selected instruments in widespread use to illustrate their comparative performance and pros and cons.

Methods

A systematic search strategy was devised and queried on Medline from 1973 to 2012 including the terms mania, hypomania, bipolar spectrum, mood spectrum, instrument, rating scale, questionnaire, interview and validity, reliability, psychometric properties.

To be included, a study had to be published in a peer-reviewed journal or book and in English.

Results

The Medline search yielded a total of 43 studies, retrieved from journal articles, describing 31 instruments, 17 self-report and 14 interview-based.

Table I summarizes the characteristics and the psychometric properties of the instruments identified, including the internal consistency, concurrent/discriminant validity, inter-rater reliability and factor structure (when applicable and when available). The assessment instruments for manic symptoms are classified according to their format (self-report or interview-based) and are sorted in decreasing order by year of publication. The seven selected instruments are in boldface.

Self-report questionnaires

The first author who strongly supported the use of self-report rating scales to assess the presence and/or severity of manic symptoms was Altman, who in 1997 developed the Altman Self-Rating Mania Scale [19], consisting of 5 items rated on a Likert scale of 0-4. In his commentary in 1998 [20], he examined the extent to which the severity of illness, the presence of psychosis or the lack of insight may threaten the reliability of a self-report measure. After comparing his measure against interview-based instruments (CARS-M, MRS), he concluded that 'self-rating mania scales are both reliable and valid for patients with manic symptoms, including those with psychotic features and those having little or no insight into their illness.'

This scale has recently gained a renewed popularity and is used in the US, together with the Quick Inventory of Depressive Symptoms (QIDS), to monitor manic and depressive symptoms over time through weekly text messages and e-mails [21 22]. These studies suggested that text message-based symptom monitoring during routine follow-up may be a reliable alternative to in-person interviews.

Among the self-report instruments developed to improve the detection of bipolar disorders, the Mood Disorder Questionnaire (MDQ) and the Hypomania Checklist-32 (HCL-32) have currently received most research attention.

Below we summarize the characteristics and psychometric properties of these 2 scales and the Bipolar Spectrum Diagnostic Scale (BSDS) and the Mood Spectrum Questionnaire (MOODS-SR), which were developed to detect softer forms of bipolar disorders or isolated symptoms of manic-hypomanic spectrum co-occurring with other axis-I disorders.

The other instruments listed in Table I include the Self-Report Manic Inventory (SRMI) and the Altman Self-rating Mania Scale (ASRM) designed specifically for assessing the manic pole of the illness and seven bipolarity rating scales: Visual Analogue Mood Scale (VAMS), Internal State Scale (ISS), Depression-Happiness Scale (D-HS), Manic Depressiveness Scale, Affective Self Rating Scale (ASRS), Hypomania Attitudes and the Positive Predictions Inventory (HAPPI) and Multidimensional Assessment of Thymic States (MAThyS). Moreover, Table I shows instruments that assess temperament, character and manic personality, the Temperament evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-A) and the Affective Temperament Questionnaire (ATQ) and two rating scales developed to assess multiple psychiatric disorders, the

Concise Associated Symptoms Tracking Scale (CAST-SR) and the My Mood Monitor (M-3) Checklist.

Mood Disorders Questionnaire

The Mood Disorders Questionnaire (MDQ), developed by Hischfeld et al. in 2002 [7 23], consists of 13 dichotomous items reflecting DSM-IV criteria for a manic episode, 1 item inquiring whether the symptoms co-occurred,and 1 item in which the subject has to evaluate on a four-point scale the extent to which manic symptom led to significant and occupational dysfunction. In a review of Zimmermann and Galione [24] across all studies carried out in adults, the sensitivity of the MDQ was 0.61, specificity was 0.87, the positive predictive value was 0.58 and the negative predictive value was 0.88. Compared to studies using the MDQ for psychiatric outpatients, studies carried out in the general population found that it had much lower sensitivity and positive predictive value, and higher specificity and negative predictive value. The MDQ's sensitivity was higher in detecting bipolar I than bipolar II disorder (0.66 vs. 0.39). Lowering the threshold to identify cases markedly improved the MDQ's sensitivity, with only a modest reduction in specificity. Studies of the best symptom cut-off to identify cases produced inconsistent findings.

Based on currently available evidence, Zimmermann and Galione's [24] conclusions were that routine clinical use of the MDQ cannot be recommended because of the absence of studies simultaneously examining both the potential benefits (e.g. improved detection) and costs (e.g. overdiagnosis) of screening.

In the Italian validation study by Hardoy and Colleagues [25], the MDQ showed a good accuracy for bipolar or schizoaffective bipolar type disorders compared with patients with other axis I diagnoses or no diagnosis: the cut-off of 6 provided the best balance of sensitivity (0.76) and specificity (0.86). The accuracy for bipolar II disorders was sufficient but not excellent. The MDQ instrument was also recently validated in Chinese by Zhaoyu Gan et al. [26]. In this study, carried out in patients with mood disorders, the MDQ showed a good accuracy for bipolar disorder: the optimal cut-off was 4, with a sensitivity of 0.72 and a specificity of 0.73. Another recent Chinese study [27] on a large sample of patients treated for major depression found that one-fifth met criteria for bipolar disorders using the MINI Neuropsychiatric Interview. In this study, the MDQ had a poor ability to discriminate patients with and without bipolar disorder (sensitivity 0.30). In conclusion, given that the selection of the optimal cut-off requires a trade-off between sensitivity and specificity and that high values on both are desirable for use in clinical practice, the MDQ appears to possess a relatively high specificity and more limited sensitivity. In other words, the MDQ has a better performance in ruling out than in confirming a diagnosis of bipolar disorder.

Hypomania Checklist-32 (HCL-32)

The HCL-32 is a self-report questionnaire developed by Angst et al. in 2005 [28] and validated in different countries and languages (German, English, Swedish, Italian, Spanish, Polish, Chinese, Korean and Portuguese) that includes a list of (hypo)manic symptoms to be rated as present or absent with reference to a period of high state. It was originally designed to identify hypomanic symptoms in patients with major depressive disorder (MDD) in order to differentiate bipolar spectrum disorder (BSD) from MDD. The total HCL-32 score is obtained by adding up the positive responses to the 32 symptoms of hypomania. In the original validation study, comparing results from Italian and Swedish samples, the HCL distinguished BSD from MDD with a sensitivity of 0.80 and specificity of 0.51 [28]. In Italy, a further validation study performed by Carta and Colleagues [29] indicated good accuracy of HCL-32 as a screening instrument for BPD in a psychiatric setting, with a low rate of false negatives, and a fairly good degree of identification of bipolar II disorder. The recommended cut-off for discriminating bipolar disorders from other diagnoses (or no diagnosis) and for discriminating bipolar II disorder was 12.

Overall, evidence about this instrument indicates that its specificity is low because values around 0.50 indicate a performance no better that chance.

Bipolar Spectrum Diagnostic Scale (BSDS)

Ronald W. Pies [30] developed the BSDS to detect milder variants of bipolar disorder. The scale consists of two parts. The first part is a paragraph containing 19 statements describing many of the symptoms of bipolar disorder. For each statement, respondents are asked to place a checkmark if they believe that the statement applies to them. The second part of the BSDS is a single multiple-choice question asking respondents how well the paragraph describes them. The sensitivity for the bipolar I group was 0.75, while the sensitivity for the bipolar II/NOS group was 0.79. In comparison, only 15% of the unipolar subjects received false-positive screens from the BSDS, indicating a specificity of 0.85 [30]. The sensitivity of the BSDS proved to be similar for bipolar I disorder, bipolar II disorder and bipolar disorder NOS / cyclothymia in a large sample of 1,100 psychiatric outpatients [31]. A receiver operating curve (ROC) analysis indicated that cut-offs of 11 and 12 maximized the sum of sensitivity and specificity for the entire group of patients with bipolar disorder (AUC = 0.80, $p < 0.001$). The cut-off point associated with 90% sensitivity for the entire sam-

TABLE I.
Psychometric properties of manic/hypomanic symptom rating scales. The seven instruments described in the text are in boldface. *Proprietà psicometriche delle scale di valutazione dei sintomi maniacali/ipomaniacali. I sette strumenti descritti nel testo sono in grassetto.*

ADMINISTRATION: SELF-REPORT							
Year	**Instrument**	**Internal consistency**	**Concurrent/ discriminant validity**	**Factor analysis**	**Description/Aim**	**Inter-rater reliability**	**References**
2011	Concise Associated Symptoms Tracking Scale Self-report (CAST-SR)	Alpha = 0.81 (17 item) Alpha = 0.78 (16 item)	The 5 CAST-SR domains correlated well with other standard measures of depressive severity and assessment of potential precursors symptoms (BAI, HDRS, PDSQ, QIDS-C)	5 factors: Irritability Anxiety Mania Insomnia Panic	The CAST includes questions about irritability, anxiety, mania, insomnia and panic domains thought to be associated with increased risk for suicide-related events and behaviours. The items in the CAST were designed to be rated using a Likert scale		54
2010	My Mood Monitor (M-3) Checklist	The M-3 bipolar module had a somewhat higher sensitivity (0.88; 95% CI, 0.77-0.95) but a lower specificity (0.70; 95% CI, 0.66-0.74). The anxiety module had a sensitivity of 0.82 (95% CI, 0.75-0.87) and a specificity of 0.78 (95% CI, 0.74-0.81), whereas the PTSD module had a sensitivity of 0.88 (95% CI, 0.74-0.96) and a specificity of 0.76 (95% CI, 0.73-0.80)			M-3 Checklist is a 23-item self-report symptom checklist that inquires whether during the past 2 weeks the patient experienced symptoms of major depressive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, PTSD and obsessive compulsive disorder. The M-3 also inquires about a lifetime history of symptoms of bipolar spectrum disorder. At the end of the symptom checklist, the M-3 poses 4 functional impairment questions. The M-3 is developed to screen for multiple psychiatric disorders in primary care		55
2009	Affective Temperament Questionnaire (ATQ)	Hyperthymia: alpha = 0.68 Cyclothymia: alpha = 0.83 Dysthymia: alpha = 0.81		3 factors: Hyperthymia Cyclothymia Dysthymia	Was designed to capture the essence of the criteria of Akiskal and Mallya (criteria defining 4 affective temperaments: hyperthymic, irritable, cyclothymic, and dysthymic) in a self-rating form	Hyperthymia and cyclothymia were more prevalent among individuals with BP than among individuals with MDD or no history of a mood disorder. Dysthymia occurred at a relatively similar rate among individuals with MDD or BP	56

2008	Affective Self Rating Scale	The subscales for mania and depression showed high internal consistency with Cronbach's alphas of 0.89 for the depression subscale and 0.91 for the mania subscale	Depression subscore MADRS (r = 0.74) HIGH-C (r = 0.15) CGI-BP-D (r = 0.68) CGI-BP-M (r = -0.01) Mania subscore MADRS (r = 0.25) HIGH-C (r = 0.80) CGI-BP-D (r = 0.10) CGI-BP-M (r = 0.73)	4 factors	Measurement of intensity of current affective symptoms (depressive manic and mixed states)		57
2008	Multidimensional Assessment of Thymic States (MAThyS)	Alpha = 0.95	The MATHYS total score is moderately correlated of both the MADRS scale (depressive score; r = -0.45) and the MAS scale (manic score; r = 0.56)	5 factors: Emotional reactivity Motivation and psychomotor function Sensory perception Interpersonal communication Cognition	Discriminate between different sub-populations among patients suffering from bipolar disorders. The instrument is designed as a multi-dimensional assisted self-administered questionnaire comprising 20 items relating to individual states as perceived by patients for the preceding week		58
2006	Hypomania Attitudes and Positive Predictions Inventory (HAPPI; 61-item version)	Cronbach's alpha ranged from 0.83 for Increasing Activation to Avoid Failure and Grandiose Appraisals of Ideation to .90 for Social Self-Criticism. Internal consistency was Cronbach's .97 for the overall scale	HAPPI was significantly and positively related to prospective ISS Activation, Conflict and Depression. There was also a negative relationship between HAPPI and ISS Well-being	Factors: Social Self-Criticism Increasing Activation to Avoid Failure Success Activation & Triumph Over Fear Loss of Control Grandiose Appraisals of Ideation Regaining Autonomy	The HAPPI was developed to assess the multiple, extreme, and personalized beliefs key to an integrative cognitive model of bipolar depression and mood swings. The model postulated that bipolar symptoms are developed and maintained by interpreting physiological, affective, and cognitive changes to internal states, and perceived behavioral changes, as having extreme personal meaning. These appraisals are multiple, positive and negative, and can therefore be conflicting		59, 60

(continues)

(Table I follows)

ADMINISTRATION: SELF-REPORT							
Year	**Instrument**	**Internal consistency**	**Concurrent/ discriminant validity**	**Factor analysis**	**Description/Aim**	**Inter-rater reliability**	**References**
2005	Hypomania Checklist-32 (HCL-32)	Alpha = 0.82 (Italian sample) Alpha = 0.86 (Swedish sample)		2 factors: Active/elated Risk-taking/irritable	The primary goal of the HCL-32 is to identify hypomanic components in patients with MDD in order to help the clinician to diagnose BP-II and other BP spectrum disorders presenting in psychiatric and general medical practice		28
2005	Bipolar Spectrum Diagnostic Scale (BSDS)	Sensitivity: 0.75 for the bipolar I group 0.79 for the bipolar II/NOS. 15% of the unipolar subjects received false-positive screens from the BSDS, indicating a specificity of 0.85			Designed to detect the milder portions of the bipolar spectrum in outpatients. The final version is composed of two parts. The first part is a paragraph containing 19 positively valenced sentences describing many of the symptoms of bipolar disorder. The second part is one simple multiple-choice question, asking subjects to rate how well the story describes them overall		30
2005	Temperament evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-A)	Alpha for the four scales: Cyclothymic 0.88 Irritable 0.84 Hyperthymic 0.81 Dysthymic 0.76		4 factors: Cyclothymic Irritable Hyperthymic Dysthymic			61
2002	Mood Spectrum Self-Report (MOODS-SR) Available in the lifetime and last-month format			11 factors: Psychomotor activation Mixed instability Spirituality/mysticism/psychoticism Mixed irritability Euphoria Depressive mood Psychomotor retardation Suicidality Drug/illness related depression Psychotic features Neurovegetative symptoms	The SCI-MOODS and the MOODS-SR includes 161 items coded as present/absent, for one or more periods of at least 3 to 5 days. Items explore depressive and manic mood, energy, and cognition, and disturbances in rhythmicity		37

2000	Mood Disorder Questionnaire (MDQ)	Alpha = 0.90			The Mood Disorder Questionnaire is a self-report, single-page inventory that screens for a lifetime history of a manic or hypomanic syndrome by including 13 yes/no items derived from both the DSM-IV criteria and clinical experience		7
1998	Manic Depressiveness Scale	The Cronbach a for the depressive items was 0.63 and for the mania items was 0.56	The subscales distinguish well between the patients and the control group		Detection of people who at some point in their lives had experienced behaviours or actions typical of bipolar disorders. This type of scale allows not only the assessment of past or present experiences with this disorder but can also be used as an indicator of cyclothymic syndromes or attenuated forms		62
1998	The Depression-Happiness Scale	Alpha = 0.88	Higher scores on the D–H S were associated with higher scores on the OHI, $r = .59$, $p < .001$, and lower scores on the BDI, $r = -.75$, $p < .001$, confirming the construct validity of the scale		This is a self-report scale which contains 25 items representing a mix of affective, cognitive, and bodily experiences. Higher scores on the scale indicate a higher frequency of positive thoughts, feelings, and bodily experiences and a lower frequency of negative thoughts, feelings, and bodily experiences		63
1997	Altman Self-rating Mania Scale	Alpha: mania = 0.79 psychosis = 0.65 irritability = 0.65	The Pearson correlation coefficient between ASRM mania subscale scores and MRS total scores was r = .718 (p < .001) and between ASRM mania subscale scores and CARS-M mania subscale scores r = .766 (p < .001)	3 factors: Mania Psychosis Irritability	Brief self-rating mania scale, compatible with DSM-IV criteria, used to measure the presence and severity of manic symptoms for research or clinical purposes		19

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(Table I follows)

ADMINISTRATION: SELF-REPORT							
Year	**Instrument**	**Internal consistency**	**Concurrent/ discriminant validity**	**Factor analysis**	**Description/Aim**	**Inter-rater reliability**	**References**
1992	Self-Report Manic Inventory (SRMI)	Alpha = 0.94	The discrimination analysis shows that the questionnaire seems to differentiate well between manic and non-manic subjects (71% of the samples are well classified) Test-retest reliability: (r = 0.93 for manic subjects and 0.73 for the whole sample	2 factors: Energized Dysphoria Hedonistic Euphoria	Includes the symptoms of mania as described in the DSM-III-R and also in some authoritative works together with the authors' experience. The 47 items contained in the scale are answered through items with true/false options. An insight question is added to these 47 items		46
1991	Internal State Scale	Alpha: from 0.81 to 0.92 on the four factors	The activation subscale gave a strong correlation with the Manic Rating Scale by Young (r = 0.60). The Depression Index correlated with that of Hamilton (r = 0.84) as did that of Wellbeing (r = 0.73)	4 factors: Depression Index Wellbeing Activation Perception of Conflict	Instrument for assessment of manic and depressive symptoms by patients and their families		64
1973	Visual Analogue Mood Scale		VAMS correlated with the SDS and several subscales of the Clyde Mood Scale The VAMS digit-symbol combination was able to distinguish patients with affective disorder from others, better than other tests used		The VAMS is a rectangular card 100 mm by 35 mm on which the following instruction is printed: 'How is your mood right now? A mark on the line toward the left represents your worst mood, toward the right, your best.' The VAMS score is determined by measuring the distance in millimetres from the left end of the card to the patient's mark		65

ADMINISTRATION: INTERVIEW-BASED							
2011	Concise Associated Symptoms Tracking Scale Clinical rating (CAST-C)	CAST-C: Alpha = 0.80 (17 item) Alpha = 0.77 (16 item)	The 5 CAST-C domains correlated well with other standard measures of depressive severity and assessment of potential precursors symptoms (BAI, HDRS, PDSQ, QIDS-C)	5 factors: Irritability Anxiety Mania Insomnia Panic	The CAST includes questions about irritability, anxiety, mania, insomnia and panic domains thought to be associated with increased risk for suicide-related events and behaviors. The items in the CAST were designed to be rated using a Likert scale		54
2009	Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)	Cronbach's alpha = 0.93	Total BRIAN scores were highly correlated with the global Pittsburgh Sleep Quality Index score (rho = 0.77, $p < 0.001$) Highly significant differences between the clinical and control group were found for the whole scale ($U = 925.5$, $p < 0.001$)	3 factor solution: Sleep/social Rhythm factor Activity factor Feeding factor	Designed to assess biological rhythms in the clinical setting		66
2007	Bipolar Inventory of Symptoms Scale (BISS)	Cronbach's alpha for the total scale was 0.90, 0.93 for the depression subscale and 0.92 for the mania subscale. Internal consistency ranged from 0.69 to 0.93 for all symptom clusters except somatic complaints (0.39)	Total BISS and manic subscale scores were significantly associated with GAF scores (-0.52, -0.48). Irritability cluster scores were significantly associated with CGI-BD and GAF scores (0.63, -0.56)as were psychosis cluster scores (0.56, - 0.67). No depression cluster or the depression subscale was significantly associated with either CGI-BD or GAF Discriminant validity: the BISS total score was significantly higher in each syndromal mood state (depressed, mixed, and manic/hypomanic) than in recovered, but did not differ between syndromes	5 factors: Mania Depression Irritability Anxiety psychosis	The BISS is designed to comprehensively assess and quantitate the symptomatology of BDs, including bipolar II and spectrum patients, and to provide a sensitive instrument for the detection of treatment effects		67

(continues)

(Table I follows)

ADMINISTRATION: INTERVIEW-BASED							
Year	**Instrument**	**Internal consistency**	**Concurrent/ discriminant validity**	**Factor analysis**	**Description/Aim**	**Inter-rater reliability**	**References**
1999	Structured Clinical Interview for Mood Spectrum (SCI-MOODS)	Internal consistency for the seven domains ranged between 0.72 and 0.92			Designed to evaluate the lifetime presence/absence of the DSM-IV core symptoms of depression and mania, atypical symptoms, subthreshold manifestations and behavioural traits that arise as a mean of coping with mood symptoms		36
1999	Coping inventory for prodromes of mania (CIPM)	Alpha: Stimulation reduction = 0.77 Problem-directed coping = 0.85 Seeking professional help = 0.53 Denial or blame = 0.70		4 factors: Stimulation reduction Problem-directed coping Seeking professional help Denial or blame	Instrument aimed at assessing how manic depressive sufferers dealt with their prodromes of mania		69
1998	Temperament evaluation of Memphis, Pisa, Paris and San Diego (TEMPS)	Alpha for the four scales: Depressive 0.85 Hyperthymic 0.86 Cyclothymic 0.94 Irritable 0.88		Four factors: depressive hyperthymic cyclothymic irritable			70
1994	Clinician-Administered Rating Scale for Mania (CARS-M)	Alpha = 0.93	Manic Rating Scale ($r = 0.94$). The sensitivity of the scale is very high, differentiating between diagnostic groups ($p < 0.001$)	2 factors. Mania (10 items). Psychoticism (5 items)	Scale for the assessment and quantification of Mania; contains 15 items rated on a Likert scale from 1 to 5, except for one which goes from 1 to 4 It is a symptomatic scale also including information culled by other members of the hospital unit or family members		71
1988	Manchester Nurse Rating Scale for Mania (MNRS-M)	All the individual items of the MNRS-M were significantly correlated with the total mania score	Correlation with Shopsin Global Mania Rating was 0.65 Correlation with YMRS was 0.79		The scale, administered from the nursing staff, was designed for the daily rating of manic ward behaviours	The product-moment correlation coefficients (r) obtained ranged from 0.813 to 0.993 ($p < 0.05$)	72
1986	Hypomanic Personality Scale		Test-retest reliability (15 weeks): 0.81		A 48-item true–false scale measuring hyperactive, ambitious, and exhibitionistic behaviours as well as feelings of euphoria and flights of thoughts		73

1978	Bech-Rafaelsen's mania scale				Clinician interview assessing the current manic symptoms; comprises 11 items defined against a five-point scale	inter-rater reliability is high (r = 0.80-0.95 for four raters)	43
1978	Young Mania Rating Scale (YMRS) Clinical interview		The total scores on the YMRS correlated highly with the global rating (0.88) and the Petterson Scale (0.89). The correlation with the Beige scale, although of a lower magnitude (0.71), was acceptable		The Young Mania Rating Scale consists of eleven items, each with five explicitly defined grades of severity. The choice of items was made on the basis of published descriptions of the core symptoms of the manic phase of bipolar affective disorder and includes those abnormalities which were felt to exist over the entire range of illness from mild to severe	The correlation between the ratings of two physicians was 0.93 for the total YMRS score and ranged from 0.66 for item 9, disruptive-aggressive behaviour, to 0.95 for item 4, sleep. All correlations were significant at the 0.001 level	39
ADMINISTRATION: OTHER							
2010	The Interactive Computer Interview for Mania (ICI-M) Computer-administered interview	Alpha = 0.82			Computer-administered interview that both presents probes designed to elicit information about the presence and severity of symptoms and utilizes a scoring algorithm to select follow-up questions and rate subject responses in accordance with rating scale anchor points The goal of the ICI is to provide a standard comparator that can be used to enhance the sensitivity and consistency of human raters by providing on-going feedback on the concordance of their ratings with the ICI ratings and identify those in need of specific remediation during the course of study operations	The intraclass correlation coefficients was 0.91 between the ICI-M and an expert consensus rating	74
2010	Observer-Rated Scale for Mania (ORSM)	Alpha = 0.89 Test-retest reliability. r = 0.76-0.89	Correlations with DSM-IV were high with a Pearson's correlation coefficient ranging from of .74 and .70 ($p < .01$). Similarly, Pearson's correlation coefficient for the YMRS ranges from .75 and .76 ($p < .01$) and for the MSS ranges from .65 and .62 ($p < .05$)	The three-factor solution accounted for 70.5% of the variance. Euphoric mania Instable mania Psychotic mania	A mania rating scale that can be used by individuals who are in close contact with the patient in order to assess mania and to determine its severity		75

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ple of patients with bipolar disorder was 8. At this cut-off, the specificity of the scale was 51.1% with a positive predictive value of 16.0%. The authors compared patients with and without bipolar disorder on each of the BSDS symptom items. The odds ratios were higher for the items assessing hypomanic / manic symptoms than those assessing depressive symptoms, although the performance of a subscale composed only of the hypomania / mania items was nearly identical to that of the entire scale (AUC = 0.81, $p < 0.001$).
Zimmermann et al. [31] concluded that this instrument is excellent at ruling out a diagnosis of bipolar disorder; however, the low positive predictive value indicates that it is not good at confirming diagnosis. These data raise questions about the use of the BSDS as a screening measure in routine clinical psychiatric practice.

Cross-validations of MDQ, HCL-32 and BSDS

In China, the optimal cut-off for the MDQ was determined as 4 symptoms endorsed and that for the HCL-32 11 symptoms. The administration of the HCL-32 coupled with the collection of family history for bipolar disorder proved to be more efficient than the MDQ to detect bipolar disorder [32].
In Italy, Carta et al. [29] examined the accuracy of HCL-32 in detecting bipolar I and II disorders compared with the MDQ. When the balance between sensitivity and specificity was considered, the MDQ had better performance in detecting bipolar disorders, although the HCL-32 was better in discriminating bipolar-II disorder.
In Spain, Vieta et al. [33] compared the discriminative capacity of the two instruments, using the HCL-32 sensitivity and specificity indices and verifying that the confidence intervals of the Spanish version of the MDQ contained the value of the HCL-32 indices. The sensitivity of the HCL-32 was 0.85 with a specificity of 0.79. The confidence intervals for the sensitivity and specificity of the MDQ were 95% CI (0.51, 0.69) and 95% CI (0.94, 0.99), respectively. Because the sensitivity and specificity values of the HCL-32 fell outside the confidence intervals of the MDQ, the authors concluded that the HCL-32 had higher sensitivity but less specificity than the MDQ. This procedure, however, appears questionable because the authors should have tested the statistical difference between the areas under the curve of the two instruments to draw a conclusion about their comparative performance.
In Poland, Rybakowski et al. [34] reported that hypomanic symptoms exceeding cut-off criteria for bipolarity by HCL-32 were present in 37.5% of patients and, by MDQ, in 20% of patients. The percentage of patients with treatment-resistant depression was significantly higher both in patients screening positive on HCL-32 and in those screening positive on MDQ compared to those screening negative, providing additional evidence of the discriminant capacity of the two instruments.
In an English study, the HCL-32 performed better than the Bipolar Spectrum Diagnostic Scale as a means of identifying bipolar disorder in primary care, although the positive predictive values of both instruments were relatively low [35].
In summary, these studies suggest that the best screening instrument is the HCL-32, because of its higher sensitivity and ability to discriminate bipolar I from bipolar II disorder.

The Mood Spectrum (MOODS-SR)

The MOODS-SR is a self-report instrument consisting of 161 dichotomous items designed to provide a careful assessment of depressive and manic/hypomanic features that may have occurred for at least 3-5 days during the individual's lifespan. The instrument was first developed in English and Italian in parallel by a panel of experts as a structured interview [36] and then as a self-report questionnaire [37]. In both formats it has been shown to have excellent psychometric properties. A recently published paper reported the results of a classification tree analysis of a pooled dataset of 1158 patients with bipolar disorders (I, II and NOS) or unipolar depression participating in 5 studies [38] who were administered the MOODS-SR.
Using 11 dimensions derived from factor analyses that characterize the manic and the depressive side of the mood spectrum (psychomotor activation, mixed instability, spirituality/mysticism/psychoticism, mixed irritability, euphoria, depressive mood, psychomotor retardation, suicidality, drug/illness-related depression, psychotic spectrum features, neurovegetative symptoms), the authors determined that only 4 of these dimensions (psychomotor activation, mixed instability, suicidality and euphoria, comprising overall 33 dichotomous items, see Table II) are needed to stratify the sample into subgroups with a differential risk of bipolarity, and identified cut-off scores for each dimension to be used in clinical practice. This paper deserves mention because it provides an empirical confirmation of the role of psychomotor activation as the key feature of bipolar disorder. This finding is in line with the recent changes proposed by the DSM-V, which revised criterion A to include increased energy/activity as a core symptom of mania.

Interview-based instruments

Among observer-rated instruments, the nurses' rating scales were the first instruments to appear, followed by specific instruments for application by clinicians.
Table I lists 12 interview-based instruments, an observer-rated instrument and a computer-administered interview.

TABLE II.
MOODS-SR items discriminating unipolar from bipolar patients. *Item del MOODS-SR che discriminano tra pazienti bipolari e unipolari.*

PSYCHOMOTOR ACTIVATION
68. Urge to communicate
69. Desire to reconnect with people
70. Talkative
71. Noisy
72. Racing thoughts
73. Too many thoughts at once
74. Shifting interests
76. Assertive
77. Vigorous
78. Very impatient
79. Constantly active
125. Irresponsible
136. More energetic with less sleep
143. Not tired even without sleeping
MIXED INSTABILITY
46. Frequently changing: job, residence, friends, hobbies
47. Risk taking
55. Irritable or elevated mood when you were abusing alcohol
56. Irritable or elevated mood when you increased your use alcohol
126. Made important decisions very rapidly
128. Tended to ignore everyday rules and social etiquette
157. More interested in sex
158. Changed sexual partners
EUPHORIA
29. Persistently good or high
30. High sense of humor and irony
31. Even the smallest thing could you very enthusiastic
32. Liked to make puns or plays on words
33. Making a lot of jokes
SUICIDALITY
102. Life is not worth living
103. Wishing not to wake up in the morning
104. Want to die or hurt yourself
105. Specific plan to hurt or kill yourself
106. Suicide attempt
107. Suicide attempt requiring medical attention

Five of these instruments are designed to assess the manic pole of the bipolar disorder (Clinician-Administered Rating Scale for Mania (CARS-M), Observer-Rated Scale for Mania (ORSM), Interactive Computer Interview for Mania (ICI-M), Young Mania Rating Scale (YMRS) and Bech-Rafaelsen Mania Scale (BRMES)) and four to assess both poles (Bipolar Inventory of Symptoms Scale (BISS), Brief Bipolar Disorder Symptom Scale (BDSS), Manchester Nurse Rating Scale for Mania (MNRS-M) and the Structured Clinical Interview for Mood Spectrum (SCI-MOODS). Moreover, in Table I two instruments assessing temperament, character and manic personality (the Temperament evaluation of Memphis, Pisa, Paris and San Diego [TEMPS] and the Hypomanic Personality Scale), a rating scale assessing multiple psychiatric disorders (Concise Associated Symptoms Tracking Scale; CAST-C), an instrument designed to assess biological rhythms in the clinical setting (Biological Rhythms Interview of Assessment in Neuropsychiatry; BRIAN) and an instrument that examines the coping strategies used by manic depressive patients during the prodromal phase of their manic episodes (Coping Inventory for Prodromes of Mania [CIPM]) are presented.
Below we list the characteristics of the two most widely used scales in clinical trials.

The Young Mania Rating Scale (YMRS)

This scale, developed by Young in 1978 [39], includes 11 items and is used to assess disease severity in patients already diagnosed with mania. It is intended to be administered by a trained clinician who assigns a severity rating on a Likert scale for each item based on a personal interview. The total score ranges from 0 to 56. The scale is based on the patient's subjective report of his/her clinical condition over the previous 48 hours that typically takes 15-30 minutes to administer. Items can be rated by querying the patients or from direct observation, and encompass elevated mood, increased motor activity, sexual interest, sleep, irritability, speech, language/thought disorder, content, disruptive/aggressive behaviour, appearance and insight. It is the most used outcome measurement in clinical trials and longitudinal naturalistic studies. A cut-off on the total YMRS score < 4 was suggested by Berk [40] to denote complete remission. Gonzalez-Pinto [41] used a cut-off > 20 for acute mania and Benvenuti et al. [42] used a cut-off of ≥ 10 to define a manic/hypomanic switch in patients with unipolar depression.

The Bech-Rafaelsen mania scale (BRMAS)

The BRMAS [43 44] is used to assess current manic symptoms and takes 15-30 minutes to administer. The 11 items are rated on a 5-point scale and each rating has very specific anchor points that facilitate the rating. The items explore

motor activity, verbal activity, flight of thoughts, voice/noise level, hostility/destructiveness, feelings of well being, self-esteem, contact with others, sleep changes, sexual interests, and work activities, similarly to YMRS, but do not assess insight and appearance. This scale has been frequently used as an outcome measure in clinical trials for more than 30 years. Studies of the internal validity of the BRMAS have demonstrated that the simple sum of the 11 items of the scale is a sufficient statistic for the assessment of the severity of manic states. Both factor analysis and latent structure analysis (the Rasch analysis) have been used to demonstrate that the scale is unidimensional. The total score of the BRMAS has been standardized so that scores between 15 and 20 indicate mild hypomania, scores between 20 and 27 indicate moderate mania, and scores ≥ 28 indicate severe mania. The inter-rater reliability has been found to be high in a number of studies conducted in various countries [45].

Discussion

Traditionally, observer-rated scales have been used to measure manic states and self-rating scales have been developed only more recently. The latter have the advantage of being able to assess the patient's internal states and avoiding possible misinterpretation of clinicians, although some authors argued that their subjective nature makes them at risk of exaggeration or understatement of symptoms and non-standard interpretations of the meaning of the questions [46].

In the experimental research context, self-report and interview-based instruments are commonly utilized for preselected patients with mood disorders who have well-established diagnoses to assess treatment outcomes in terms of response/remission [30 47-49]. In contrast, in routine clinical practice no one would argue that rating scales eliminate the need for a competent psychiatric evaluation, considering that there are no 'special questions' on the most widely used scales that are unfamiliar to a competent clinician [50]. Nonetheless, rating scales may be very useful in clinical practice when it comes to making sure that specific and standardized questions (e.g. suicidal ideation) are consistently asked and recorded. Moreover, evidence that the administration of rating scales might improve the efficiency of diagnostic evaluation outside clinical trials (characterized by well-defined inclusion/exclusion criteria) is still controversial [30 28 51]. In particular, two potential negative consequences have been commonly reported with the systematic assessment provided by self-rating scales for mania in clinical settings. On the one hand, the sensitivity of several instruments is around 60-65%, and clinicians who rely on screening scales that use the first stage in a two-stage process for diagnosing bipolar disorders are at high risk of missing the correct diagnosis in approximately one-third of patients. On the other hand, the positive predictive value of such instruments is often inadequate, raising the possibility of an over-diagnosis of bipolar disorder, if no more valid and comprehensive diagnostic assessment tools are subsequently provided.

In developing a broad-based screening measure for multiple psychiatric disorders, Zimmermann and Mattia [52] recommended that a cut-off resulting in diagnostic sensitivity of 90% and a correspondingly high negative predictive value be chosen when using an instrument in clinical practice. With high negative predictive value, the clinician can reliably assume that when the test indicates that the disorder is not present, inquiring about the disorder's symptoms is pointless. Our review of self-report instruments indicates that this sensitivity level is not achieved by the MDQ, the HCL-32 or the BDRS and, if it is achieved, this happens at the cost of very high false positive rates. In general, the trade-off between sensitivity and specificity depends on the disease and the specific purpose of the screening. In the case of bipolar disorder, early identification of patients suffering from this condition is as important as excluding this diagnosis to develop a suitable treatment strategy.

The psychometric properties of the instruments reviewed suggest that the MDQ might be useful for screening patients presenting with recurrent depression or anxiety to rule out the presence of bipolar disorder in psychiatric clinical settings and primary care. The HCL-32, which is more sensitive than the MDQ, might be used to screen potential cases to be further investigated with a diagnostic interview. On this note, it should be emphasized that other elements such as family history, age of onset of symptoms, course of symptoms and previous response to medication play a key role in the diagnostic process.

Considering the MOODS-SR, the instrument is relatively long, which makes it more suitable for research purposes than for routine clinical use. Still, the 33 items exploring the key features discriminating bipolar disorder from unipolar depression seem to be promising as a stand-alone screening instrument to detect the presence of manic/hypomanic features lasting at least 3-5 days in the lifetime. However, to date no study has provided evidence of the psychometric properties of this subset of items.

The 5-item Altman Mania Rating Scale appears to be useful for monitoring the longitudinal course of mania/hypomania symptoms for research and clinical purposes and generates results similar to those of other longitudinal studies of bipolar disorder that use traditional retrospective, clinician-gathered mood data [21].

Regarding the interview-based instruments, the YMRS and the BRMAS have a similar coverage, although the

YMRS is to be preferred over the BRMAS because it includes an item on insight. In fact, when the severity of symptoms affects the level of insight, the reliability of the assessment may be compromised.

In conclusion, although no instrument can replace the need for accurate clinical diagnosis based on patient history, we argue that the increasing use of self-report instruments to screen bipolar disorder in high-risk patients presenting with depression or to monitor mania/hypomania symptoms over time may contribute to increasing the use of routine standardized assessment. Measurement-based treatment as the standard of care has the potential to transform psychiatric practice, move psychiatry into the mainstream of medicine, facilitate integration between primary care and mental health services [53] and ultimately improve the quality of care for patients with psychiatric illness [54].

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La terapia elettroconvulsivante nella depressione resistente: una casistica di 25 pazienti

Electroconvulsive therapy in resistant depression: a case series of 25 patients

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Summary

Objectives

The electroconvulsive therapy (ECT) is a non-pharmacological somatic treatment whose effectiveness has been demonstrated for patients suffering from severe and resistant depression (i.e. cases in which patients do not respond adequately to antidepressant treatment). It is estimated that Treatment Resistant Depression occurs in up to 30% to 40% of depressive episodes adequately treated with first-line antidepressant therapy in psychiatric setting. Treatment Resistant Depression results in disproportionate burdens, escalating medical and mental health care costs, clinicians time, and personal suffering.
Several studies demonstrated ECT's efficacy in different subgroups, such as patients with bipolar depression, mixed state, psychotic features and suicidal ideation.

Methods

We report a case series of 25 patients with treatment-resistant major depression who received ECT at the psychiatric unit of Casa di Cura "Villa Serena", Città Sant'Angelo. The subjects included in the study had at least 18 years of age and met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), for a major depressive episode associated with major depressive disorder (MDD) (n = 11, 44%), bipolar disorder (BP) (n = 11, 44%) and schizoaffective disorder (n = 3, 12%).
The group consisted of 8 men and 17 women with a mean age ± SD of 53.72 ± 13.88 years and with a mean age of onset of 32.12 ± 14.16 years.
9 patients (36%) had a temperament hyperthymic, 7 (28%) depressive, and 9 (36%) anxious. 11 patients (44%) had a history of suicidal behavior.
Patients have been evaluated before treatment, one week, 6 months and 1 year after the treatment with a global clinical assessment (CGI).

Results

Clinical evaluations made a week after the ECT showed a clinical improvement overall in 10 patients (90%) with a diagnosis of depressive disorder, 7 (63%) with bipolar disorder and 3 (100%) with schizoaffective disorder. The same evaluation repeated 6 months and 1 year after the ECT reaffirmed a global clinical improvement in 8 patients (72%) with a diagnosis of depressive disorder, 6 (54%) with bipolar disorder and in 1 subject (33%) diagnosed with schizoaffective disorder.

Conclusions

Electroconvulsive therapy appears to be effective in determining the overall clinical improvement in treated subjects. All subjects with depressive temperament show an improvement in global clinical assessments at all the three post-treatment evaluations. In particular, in our sample there were no differences in outcome due to diagnostic subgroup belonging, to presence or absence of suicidality and to temperamental characteristics.
These conclusions are, however, limited by the experimental design and therefore liable to many uncontrolled variables.

Key words

Electroconvulsive therapy (ECT) • Treatment-resistant depression • Global clinical improvement

Introduzione

La depressione resistente (DR), pur priva di una definizione soddisfacente e uniformemente accettata, ha ricevuto negli ultimi anni un'attenzione crescente da parte di clinici e ricercatori [1]. I dati della letteratura riportano che il 30-50% circa dei pazienti con diagnosi di depressione maggiore non risponde in maniera soddisfacente al primo trattamento con antidepressivi. Studi di follow-up rivelano come dal 10 al 25% dei pazienti risulti ancora sintomatico a due anni dall'esordio del disturbo [2 3]. Infine, anche dopo molteplici interventi terapeutici, fino al 10% dei pazienti presenta sintomi depressivi residui [4].
Oggetto di dibattito è la definizione operativa di DR al trattamento; sono stati, infatti, utilizzati criteri diversi per definire il numero e il tipo di trattamenti farmacologici

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inefficaci per giungere alla diagnosi di DR; per la determinazione dell'adeguatezza al trattamento (dose di farmaci e durata di somministrazione); per la definizione di risposta al trattamento ed, infine, per la valutazione della diagnosi principale e di quelle in comorbidità [5].
Alcuni autori [6 7] hanno proposto di distinguere una resistenza "relativa" al trattamento dalla resistenza assoluta. Per resistenza relativa si intende la mancata risposta alla dose media terapeutica di uno specifico antidepressivo (per esempio, nel caso dei triciclici, 200 mg/die di imipramina o equivalenti e, nel caso degli inibitori selettivi del reuptake della serotonina (SSRI), 50 mg/die di sertralina o equivalenti) somministrata per un periodo minimo di tempo utile (4 settimane). Una resistenza relativa a un trattamento implica che alcuni pazienti potrebbero rispondere se venissero curati con dosi più alte del farmaco e/o per un periodo più lungo. È stato quindi proposto di definire resistenza assoluta la mancata risposta a un antidepressivo somministrato per un periodo di tempo prolungato (per esempio, 8 settimane), alla dose minima giornaliera tollerata (per esempio, 300 mg/die di imipramina o 200 mg/die di sertralina), con una *compliance* confermata, quando possibile, dai livelli plasmatici.
Questa condizione è stata definita da altri autori con il termine di depressione refrattaria al trattamento [8].
Nell'ultimo decennio sono stati proposti numerosi metodi di classificazione dei quadri depressivi resistenti al trattamento, per cercare di individuare gruppi di pazienti non responsivi il più possibile omogenei tra loro, così da poter essere studiati nelle ricerche biologiche e cliniche. Ogni criterio di classificazione prevede il soddisfacimento di specifici criteri (numero dei trial antidepressivi effettuati, tipo di farmaco impiegato, dosaggio e durata del trattamento) prima che il paziente venga definito resistente al trattamento e classificato in base a livelli crescenti di gravità.
I modelli più utilizzati in letteratura sono: il modello di stadiazione di Thase e Rush [9]; i criteri operativi per la DR di Souery (o modello di stadiazione europeo) [10]; modello di stadiazione del *Massachussetts General Hospital* [11].
La terapia elettroconvulsivante (TEC) è un trattamento non farmacologico la cui efficacia è stata ampiamente dimostrata per i pazienti affetti da depressione grave e refrattaria [12-14]. La seconda edizione delle linee guida dell'*American Psychiatric Association* (APA) *Task Force* per la TEC [15] suggerisce l'uso della TEC in pazienti con diagnosi di depressione che mostrano una mancata risposta o intolleranza ai farmaci antidepressivi, una buona risposta a una TEC precedente, e la necessità di una risposta rapida e definitiva.
Secondo le linee guida del *National Institute for Health and Clinical Excellence* (NICE) l'utilizzo della TEC è consigliato in soggetti con disturbo depressivo grave, catatonia o episodio maniacale prolungato o severo che mostrano una mancata risposta ad adeguati trattamenti farmacologici precedenti e/o quando la condizione è ritenuta potenzialmente pericolosa per la vita [16].
Diversi studi sulla TEC hanno dimostrato la sua efficacia in diversi sottogruppi, quali i pazienti con depressione bipolare [17], stato misto [18], caratteristiche psicotiche [19] e ideazione suicidaria [20].

Metodi

Riportiamo una casistica di 25 pazienti affetti da depressione maggiore resistente al trattamento che hanno ricevuto TEC tra dal 2006 al 2010 presso l'unità operativa di psichiatria 2 della Casa di Cura "Villa Serena" di Città Sant'Angelo, Pescara.
L'unità operativa è costituita da 18 posti letto e negli anni considerati ha effettuato 1539 ricoveri. Nel periodo considerato sono stati trattati con TEC 25 pazienti pari all'1,62% del totale dei pazienti ricoverati.
I soggetti inclusi nello studio avevano almeno 18 anni di età e rispettavano i criteri del *Manuale Diagnostico e Statistico dei Disturbi Mentali*, quarta edizione (DSM-IV), per un episodio depressivo maggiore associato a disturbo depressivo maggiore (DDM) (n = 11, 44%), disturbo bipolare (BP) (n = 11, 44%) e disturbo schizoaffettivo (n = 3, 12%).
Le diagnosi sono state effettuate da uno psichiatra "esperto" secondo i criteri DSM-IV. Tutti i soggetti hanno dato il loro consenso informato scritto per ricevere la TEC.
Tutti i pazienti erano non-responder ad almeno 3 trattamenti farmacologici differenti e adeguatamente condotti negli ultimi 6 mesi.
L'apparecchio utilizzato era un Thymatron System IV, Class 1, Type BF con stimolo a onde quadre ultrabrevi (0,25 ms), capace di registrare l'EEG e l'EMG. L'ECG veniva registrato dal monitor per anestesia. Le applicazioni sono state tutte bilaterali con posizione degli elettrodi in sede temporale. La durata delle convulsioni è stata di almeno 25 secondi. L'anestesia è stata effettuata con propofol 2 mg/kg e il blocco neuromuscalare con succinilcolina 1 mg/kg. La somministrazione di ossigeno è stata eseguita prima e dopo il trattamento. Ai pazienti in terapia con sali di litio e anticonvulsivanti, i farmaci venivano sospesi 24 ore prima del trattamento con ECT e somministrati nuovamente dopo il trattamento. Tutti i trattamenti sono stati effettuati presso la Casa di Cura "Villa Serena" in ambiente attrezzato per l'anestesia e rianimazione. Tutti i pazienti prima del trattamento venivano resi edotti sul tipo di trattamento e dovevano firmare un consenso informato, che poteva essere ritirato in qualunque momento. *Ogni paziente è stato sottoposto a 3 stimolazioni per settimana, effettuati a giorni alterni.*
Il numero medio di ECT è stato simile nei 3 sottotipi diagnostici (valore modale = 6).

TABELLA I.
Caratteristiche cliniche dei pazienti con DR trattati con ECT. *Clinical features of patients with resistant depression treated with ECT.*

Diagnosi	N (%)	Risposta attuale Sì/No	Risposta a 6 mesi Sì/No	Risposta 1 anno Sì/No
Disturbo depressivo	11 (44 %)	10/1	8/3	8/1
Disturbo bipolare, episodio depressivo	11 (44 %)	7/4	6/4	6/3
Disturbo schizoaffetivo	3 (12 %)	3/0	1/2	1/2
Temperamento*				
Ipertimico	9 (36 %)	6/3	4/4	4/2
Depressivo	7 (28 %)	7/0	7/0	7/0
Ansioso	9 (36 %)	7/2	4/5	4/4
Suicidalità*				
Sì	11 (44 %)	10/1	9/2	9/2
No	14 (56 %)	10/4	6/7	6/4

* chi quadro ns

I pazienti sono stati valutati prima del trattamento, una settimana, 6 mesi e 1 anno dopo la TEC valutando il miglioramento clinico globale (CGI) [21].

Risultati

Il gruppo era composto da 8 uomini e 17 donne e aveva un età media ± SD di 53,72 ± 13,88 anni, con un'età media di insorgenza della malattia di 32,12 ± 14,16 anni. Nove pazienti (36%) presentavano un temperamento ipertimico, 7 (28%) depressivo e 9 (36%) ansioso. Undici pazienti (44%) avevano una storia di comportamenti suicidari.

Va rilevata nel nostro campione un'insolita alta percentuale di temperamento premorboso depressivo rispetto a quanto riscontrato in altri studi [22 23]. *Questo effetto di campionamento può spiegarsi con il fatto che la struttura clinica rappresenta un centro di riferimento terziario e quindi il campione è soggetto a bias dovuti all'invio di pazienti particolarmente complessi e non è un campione strettamente "consecutivo".*

Le valutazioni cliniche effettuate una settimana dopo la TEC hanno evidenziato un miglioramento clinico globale in 10 pazienti (90%) con diagnosi di disturbo depressivo, 7 (63%) con DB e 3 (100%) con disturbo schizoaffettivo. La stessa valutazione ripetuta 6 mesi e 1 anno dopo la TEC ha riconfermato un miglioramento clinico globale in 8 pazienti (72%) con diagnosi di disturbo depressivo, 6 (54%) con DB e in 1 soggetto (33%) con diagnosi di disturbo schizoaffettivo (Tab. I). *La comorbidità per disturbi d'ansia non veniva valutata. È verosimile che tale comorbidità potrebbe aver influenzato la risposta al trattamento.*

Conclusioni

Tutti i soggetti con temperamento depressivo mostrano un miglioramento clinico globale alle tre valutazioni effettuate dopo il trattamento nell'arco di 1 anno (Tab. I).

In particolare nel nostro campione non vi erano differenze di esito in relazione al sottogruppo diagnostico, alla presenza o meno di suicidalità e alle caratteristiche temperamentali.

La TEC sembra essere efficace nel determinare un miglioramento clinico in soggetti con episodio depressivo maggiore resistente ai trattamenti. *Tali conclusioni vanno però limitate dal disegno sperimentale di tipo osservazionale e quindi soggetto a numerose variabili non controllate.*

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New therapeutic approaches in alcohol dependence: reduction of consumption as a step in the therapeutic goal

Nuovi approcci terapeutici nei disturbi correlati all'uso di alcol: la riduzione del consumo come step terapeutico

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Summary

Objectives

Disorders related to the abuse of alcohol should be considered as a social and health emergency. The alcohol dependent patient runs the risk of developing physical, psychological, social, economic and legal problems. Thus, there is a need to find new therapeutic strategies for the treatment of alcohol dependence. Abstinence has always represented the elective therapeutic approach in alcohol dependence; nevertheless, considering abstinence as the only successful result in clinical treatment does not allow capturing significant aspects in consumption patterns of patients. From the literature, significant results have emerged regarding reduction of alcohol consumption in terms of frequency and quantity, which can become a marker of clinical progression towards abstinence.

Methods

The present is an in-depth analysis of the existing literature (from 1962 to 2012) on possible therapeutic interventions in the treatment of alcohol dependence. The literature focuses on the relationship between "reduction of consumption versus abstinence", with both representing possible treatments in alcohol dependence.

Results

The results of a large body of research seem to agree in emphasizing a linear correlation between systemic exposure to alcohol and morbidity and mortality. On the other hand, the scientific evidence does not indicate precise and identifiable thresholds for the damage incurred from ethanol. In the light of the available data, the concept of reduction of alcohol consumption versus abstinence has become useful from clinical, social and economic aspects. The opportunity to reduce risk and organ damage, to involve the patient in a therapeutic program towards abstinence, to prevent the development of alcoholism into more severe forms and to reduce the social and economic impact are important indicators that can be achieved considering the therapeutic strategies examined.

Conclusion

From analysis of the literature, it is possible to understand that reduction of alcohol consumption can be an intermediate valid goal both therapeutically and socially, and acceptable for those patients unable or unmotivated to achieve abstinence, in order to reduce the clinical risks associated with heavy drinking. During treatment there is an important and active dual role of both the doctor and patient who should share common goals resulting from accurate analysis of the motivation and personological characteristics of the patient. New pharmacological strategies can be useful to reach this therapeutic goal. Nalmefene, a modulator of the opioid system with antagonist activity on opioid mu and delta receptors and partial agonist activity on kappa opioid receptors, appears to be especially effective in reducing ethanol consumption.

Key words

Abstinence • Alcohol Dependence • Heavy drinking • Reduction of alcohol consumption • Morbidity • Mortality • Nalmefene

Introduction

Even if the scientific community retains that achieving abstinence is still the primary objective for patients affected with alcohol abuse disorders, there is growing knowledge about the therapeutic limits of this concept. Considering abstinence as the only possibility of clinical-therapeutic success does not take into account significant aspects of alcohol consumption models. Increasing awareness of the patient means creating a cognitive path of change where reduction in consumption, in terms of frequency and quantity, can become an indicator of clinical progression towards abstinence. Individual (biological, personal, cognitive, relational) and cultural characteristics of the patient, and the course of the pathology related to alcohol dependence, allow the identification of therapeutic steps in reducing consumption that progressively lead to a condition of awareness of abstinence.

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The concept of reduction of alcohol consumption in rehabilitative paths

The social and economic costs of alcohol-related pathologies are extremely high in terms of morbidity and mortality. In the US, 4% of the adult population, over a one year period, suffers from alcohol dependence [1 2]. Alcoholism seems to be one of the most important public health problems, and worldwide is the fourth cause of disability [3]. The alcohol dependent patient can develop physical, emotional, social, financial and legal problems. In Italy, the mean annual consumption per person is 8.02 litres, which is lower than mean consumption in other European countries (Spain 10.03 litres, Greece 13.24 litres, France 13.24 litres; data from 2011). In Italy, in total, there are 36.4 million occasional and daily drinkers, and among these there are 8.18 million drinkers at risk considering non-moderate drinking and binge-drinking. It is estimated that there are about 1 million alcohol dependent individuals in Italy [4]. Of these, only 58,122 are seen by Health Services for Dependent Pathologies [5] (Fig. 1).
Considering this, there is considerable need to find new therapeutic strategies for this pathology. In this regard, an elective course for cure has always been considered the road to abstinence. However, for several years, multiple authors, analyzing the results of many studies, have taken into consideration other therapeutic alternatives [6]. One such alternative is reduction of alcohol consumption to return to 'moderate', 'controlled' or asymptomatic' use [7]. Reducing consumption is an approach to public health that is part of a larger intervention in reducing damage with the aim of limiting the negative consequences of alcohol abuse, for both the drinker and the community, by encouraging and reinforcing alternative behaviours [8]. An approach involving reduction is accepted by and encouraged in the UK [9], in Europe, and in part by Australia Canada [10-12]. In the US, however, abstinence is the preferred course for alcohol dependent individuals. Lately, there has been some discussion regarding treatment of alcohol dependence, considering a continuum of abstinence, reduced consumption and abuse (Fig. 2).
In the past, from a scientific point of view, there has been ample discussion on this subject [14]. For some authors, when dependence appears, the subject no longer has control over alcohol consumption, and thus the only possible way to halt the disease is through abstinence. Others however, have taken into consideration the possibility of adopting a strategy towards reduction in consumption. This type of strategy takes into account the different types of alcoholism and, consequently, favours a personalized approach to treatment [15]. Connors [16] noted that, even in the 1940s, following the course of patients under cure for alcoholism, a subgroup of individuals could be identified that were able to resume alcohol use after a period of abstinence, without any apparent difficulty [17-19]. In this regard, the study of Davies should also be mentioned [18], who observed that of 93 alcohol dependent subjects, 7 drank in a reduced manner after a follow-up of 7-11 years. Of these 7, only one maintained the ability to drink moderately during later follow-up. Even the results of the Rend Report [17], a longitudinal study on treated alcoholics, showed that after 18 months some patients had began controlled consumption of alcohol. Another study carried out on 70 individuals subjected to abstinence or reduction therapy showed that in both treatment groups the consumption of alcohol decreased (4 drinks/day *vs*. 10, 3 drinks/day *vs*. 5, respectively), and was maintained at two years of follow-up [20].

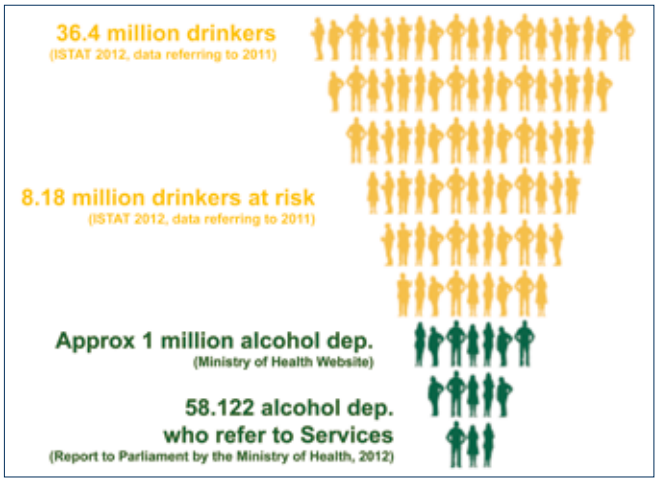

FIGURE 1.
Drinkers and alcohol dependent individuals in Italy [4]. *Bevitori e alcolisti in Italia* [4].

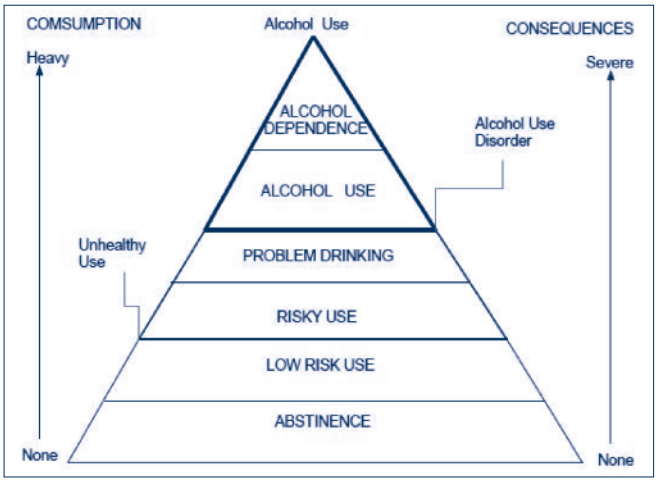

FIGURE 2.
Alcohol consumption spectrum (from Saitz, 2005, p. 598) [13]. *Lo spettro del consumo di alcol (da Saitz, 2005, p. 598)* [13].

One study considered 4 groups of subjects (N = 99) that were followed-up at 3, 5, 7 and 8 years [21]. Of these, 14 subjects presented asymptomatic drinking behaviour, and did not show signs of dependence or negative consequences. Of these 14 individuals, 10 had received a diagnosis of alcohol dependence. Considering this study, it is possible to think that some patients may be able to maintain controlled consumption of alcohol without returning to excess [7]. This may be possible based on individual characteristics such as: young age, sex (women appear more able to reduce consumption), social and psychological stability, less severe dependence [22-26], are employed and have confidence in one's ability to moderate consumption. On the other hand, abstinence is considered elective treatment for patients who are less motivated to resume non-abstinence, in the presence of medical or psychological conditions caused by continuous use of alcohol, for patients under pharmacological therapy that is dangerous in combination with alcohol, for subjects that present with severe alcohol dependence and a history of previously failed attempts at controlling substance abuse behaviour [27]. Reduction in consumption is also contraindicated in women who are pregnant or breastfeeding [27].

Considering that with alcohol dependent patients it is not simple to construct a therapeutic alliance due to the severity of the problem or the tendency to deny/minimize the problem, intuition and experience of the physician are important as he/she must be able to understand the personological functioning of the subject, and propose ad hoc treatment considering both the limits and resources available. During treatment, in addition to the physician, even the patient must have an active role. In this regard, a therapeutic alliance between the patient and physician can have significant advantages in terms of establishing treatment objectives, understanding the motivation of patients and reducing drop-outs. The formulation of a functional therapeutic course should be preceded by thorough analysis of the questions that allow negotiation of a treatment plan that considers the expectations of both the individual and the physician. In this regard, some studies have shown that patients who are presented more than one treatment alternative are more likely to become involved in therapy.

This was demonstrated by a longitudinal study [28] on 106 alcohol dependent individuals who were given the opportunity to choose between abstinence and moderate consumption. Initially, 46% of subjects (N = 49) chose abstinence while 44% (N = 47) initiated a course towards controlled consumption. After 4 weeks of treatment, 89% (N = 42) of subjects who chose abstinence reached their goal compared to 51% (N = 24) of those who chose moderate consumption (three subjects were lost to follow-up). The authors also showed that after the first 4 weeks of treatment, 49% (N = 23) of subjects that chose moderate consumption were willing to choose abstinence. On the other hand, those who initially chose abstinence could consider reduction in consumption, if this was tolerated. Even a controlled study in New Zealand [29], in which dependent subjects were allowed to choose what they felt was the most appropriate treatment, revealed a greater predisposition to abstinence. This suggests that reciprocal agreement between the patient and caregiver facilitates a realistic treatment goal.

In conclusion, according to these studies, it can be deduced that the choice of controlled consumption is a therapeutic strategy that can increase the proportion of individuals willing to accept treatment. This is significant considering the fact that less than 10% of individuals with alcohol abuse and dependency problems undertake cure [23]. Therefore, greater flexibility may help to create a therapeutic alliance and achieve a positive result. Establishing a contract with the patient, especially with those who manifest doubt and resistance, can thus be beneficial. For example, subjects can be supported by a physician to remain abstinent for 3 months with the subsequent possibility to resume moderate consumption. Another approach foresees that the patient reduces consumption with the possibility to initiate abstinence at any time, whenever it is deemed necessary [30].

Offering the possibility of choice and renegotiation appears to provide additional functionality to the patient with alcohol dependence [31]. Such a choice allows attributing an active role in the healing process, without losing sight of the objectives and motivation as related to the characteristics of the individual. In terms of treatment, recognition of the patient's choice by the physician seems vital. If the physician retains that reduction of consumption is an alternative, then even the patient will consider this as a possibility. With the aim of reducing prejudices, which even physicians have when considering reduction, it would be a significant advance to develop guidelines that include non-ambiguous parameters to define reduction. This would comprise, for example, consensus concerning what is considered a standard drink keeping in mind the quantity and frequency of consumption [32], and a shared and contingent plan for intervention and strategies for negotiation with the patient [7]. There is still a lack of agreement on these issues.

According to the US Department of Agriculture [33] and US Department of Health and Human Services [34], moderate drinking is defined as 1 drink/day for women, 2 for men and 1 per day for men and women over the age of 65 years. For others, moderate consumption is defined as 3 drinks/day and < 12 drinks/week for women, 4 drinks/day and < 16 drinks/week for men; 1 drink/day and < 8 drinks/week for individuals over the age of 65 years [35]. The existing literate has defined parameters that

allow considering one a heavy drinker on the basis of the amount of alcohol consumed, and is ≥5 drinks/day for men, and ≥4 drinks/day for women [36-40]. The consumption of more than one drink per hour and to drink according to predefined habits (in the same place with the same people at the same time) should also be considered significant. Individuals need guidance so that consumption of alcohol does not become a coping strategy, to not drink and drive, and to not drink during pregnancy or while breastfeeding. By educating individuals to not consume alcoholic beverages in a continuous manner, keeping a diary of what, how much and where alcohol is consumed, can be useful to monitor the subject's relationship with alcohol.

The studies examined allow greater critical reflection on possible therapeutic alternatives for alcohol dependence. From the available data, it is possible to think about the fact that treatment aimed at reduction in consumption can be part of the cure of alcoholism. Reduction and abstinence should not be viewed as irreconcilable strategies for intervention, but can be seen as parts of a continuum, as options of choice that are both aimed at cure, keeping in mind the personological functioning of the patient. A dependent individual, in order to initiate treatment with motivation, needs to confront the physician considering present needs in relation to the severity of the disease and individual as well as other resources available. For the subject to be able to choose the course of treatment is a predictive factor for better adherence. Moreover, the possibility to negotiate the treatment course and modify it according to individual needs, difficulties and improvements during treatment seems to facilitate a good outcome. One strong point that emerges from the above-cited literature concerns the ability of the physician to individuate the motivations of the patient and engage him/her in the therapeutic plan. Understanding the severity of the dependence and asking for help allows the physician to choose the most effective treatment. In addition, a good therapeutic alliance should be considered as essential to all types of treatment.

Relationship between excessive drinking and morbidity and mortality: reduction in consumption *versus* abstinence

Many epidemiological studies have demonstrated a close relation between excess consumption of alcohol (heavy drinking) and damage to health, automobile accidents and organ damage [41]. High levels of alcohol consumption (men: > 60 gm/day; women: > 40 gm/day) are associated with a high clinical risk for health complications [42]. Monitoring the quantity and frequency of consumption has provided accurate scientific evidence on the relationship between morbidity and mortality in the spectrum of alcohol use [43]. In a meta-analysis of 156 studies involving 116,702 subjects, it was shown than increasing the daily dose of alcohol increased the risk of organ damage, and in particular for 15 pathologies [44]. Other studies have documented a linear relationship between breast cancer and excess consumption of alcohol, and the risk progressively increased by 9% for every 10 gm of alcohol over 60 gm/day in women [45]. Concerning the female population, it would appear that gender is a positive predictive factor for the possibility to reduce consumption. In one study, 52 males and 38 females with problems of alcohol dependence were enrolled. Three months after treatment the percentage of subjects with moderate consumption was significantly higher in females than in males (75% *vs*. 35%, respectively). At one year, women had achieved more success than men in going from excessive to controlled consumption [46].

Excessive consumption is an individual phenomenon, but is often interpreted as a condition that is influenced by cultural aspects on a community level. Extensive research has shown that where there are conditions that permit excessive consumption of alcohol, there is a linear correlation with traffic accidents, violent acts and hospitalization [47].

Other studies have evaluated the therapeutic opportunity of reduction versus abstinence [18 17], and many investigations have compared abstinent and non-abstinent patients. Subjects had to control and monitor a variety of clinical conditions including: instructions for self-monitoring of blood alcohol concentration (BAC), counselling, education about alcohol-related problems, adverse conditions such as electric shock to the fingers and watching video registrations of oneself. The results of these studies have allowed for the consideration that reducing consumption of alcohol is a valid therapeutic option. Other meta-analyses have identified the clinical characteristics of patients eligible for treatment aimed at reducing alcohol consumption. These include female gender, age between 20-30 years, good psychopathological condition, social and job stability, and good cognitive preservation [7 25].

Many investigators have identified and monitored several indicators such as the period of time in going from moderate to excessive drinking, and the number of daily episodes of excessive drinking [48]. Other studies have added new variables, such as the number of days of consumption and the percentage of days of excessive consumption to achieving complete abstinence. For example, the MATCH project [49] used the combination of the percentage of abstinent days and excessive consumption compared to moderate consumption. The COMBINE [50] study utilized the combination of the percentage of abstinent days and the time between the first episode of excessive consumption of alcohol.

Such a heterogeneity of outcome measures represents the diverse forms of alcoholism and allows for reflection on the limitations of categorical approaches based only on the achievement of abstinence. A reduction in the consumption of alcohol produces new neuroadaptations in gratification circuits that maintain dependence. Phenomena of synaptic plasticity and improvement in the connectivity between neurons in the prefrontal cortex, nucleus accumbens, hippocampus and amygdala favour neurocognitive recovery of executive control. These phenomena have an impact on overall mental functioning with reordering of behaviour, attenuation of psychopathological elements induced by alcohol and greater adherence to therapy. Controlled/moderate drinking can be viewed as a final therapeutic objective, but also as a therapeutic passage towards complete abstinence.

Therapeutic prospects

With reduction of consumption versus abstinence in mind, it is worthwhile considering the available pharmacological and psychotherapeutic therapies. The former target modulation of the 'craving' dimension and reduction of the awaited gratification (positive reinforcement). Craving is a psychopathological condition characterized by irresistible desire to assume a substance. An unsatisfied desire can lead to physical and psychological suffering. Craving is defined as a status of the nervous system consequent to an adaptation to alcohol which alters the normal will of the individual that forces consumption of alcohol in spite of the knowledge of the damage it is causing [51]. From a neurobiological point of view, the craving dimension is sustained by alteration in the GABAergic/glutamatergic, dopaminergic, serotoninergic and opioidergic systems. The psychobiological model developed by Verheul [52] has three main types of craving that have different diagnostic and therapeutic approaches. The typology of the characteristics related to craving for alcohol allows individuation of the different subtypes of alcoholics. Craving reveals the neurobiological adaptation of the gratification circuits induced by alcohol. Several authors have suggested specific pharmacological therapy for the three subtypes of craving defined by the psychobiological model. In particular, they suggested naltrexone and sodium oxybate for reward craving; acamprosate, baclofen and sodium oxybate for relief craving; and an SSRI, baclofen, topiramate and ondansetron for obsessive craving [53].

Modulation of craving is needed to attenuate the abstinent symptomology induced by a reduction in consumption, to stabilize a new, more functional neurobiological structure towards controlled use of a substance and favour adherence. During the course of reduction of consumption, modulation of craving is a fundamental strategy. The pharmacological aspect is important, but correct information on how to recognize, confront and deal with craving is also needed.

Another means to favour reduction in alcohol consumption is to reduce the awaited gratification (positive reinforcement). The acute use of alcohol stimulates the release of beta-endorphins, encephalin and dynorphin [54]. The beta-endorphins and encephalin bind to endogenous opioid receptors mu (MOR) and delta (DOR) which mediate, respectively, the euphoric effects and positive reinforcement of alcohol [55]. Dynorphin, on the other hand, binds to opioid receptor kappa (KOR) and mediates the aversive effects related to the consumption of alcohol [56]. The KOR/dynorphin system is diffusely distributed throughout the central nervous system, and is implicated in several physiological and pathophysiological conditions related to behaviour and motivation [57]. This condition identifies the KOR/dynorphin system as a therapeutic target for neuropsychiatric disturbances [58]. In alcohol dependence, the KOR/dynorphin system is hyperactivated, and is responsible for the dysphoric/anhedonic symptomology. This phenomena contributes to the effects of negative reinforcement induced by alcohol [59]. In fact, in chronic alcohol dependence the response of opioid receptor mu is attenuated, while the response of the kappa receptors is increased [60]. This neuroplasticity induced by alcohol on the KOR/dynorphin system and how this neuroadaptivity can contribute to the pathophysiology of alcohol dependence is significant, and represents a potential therapeutic target for the cure of alcoholism.

A neuromodulator of the opioid system, namely nalmefene, has been investigated in a multicentre, randomized, placebo-controlled study, using nalmefene-as-needed [61]. Nalmefene is a modulator of the opioid system with antagonist activity on opioid receptors mu and delta, and partial agonist activity on opioid receptor kappa [62]. The mechanism of action proposed for nalmefene is to reduce the reinforcing affects of alcohol, and it can be used in patients who have decided to reduce the consumption of alcohol. The study showed a clinical benefit for nalmefene-as-needed in patients with alcohol dependence. Nalmefene was superior to placebo in reducing excessive consumption of alcohol (measured with heavy drinking/days) and total alcohol consumption at month 6. A significant reduction of the number of heavy drinking/days and total consumption of alcohol was observed from the first month, which was maintained throughout the duration of the study. Overall, the total consumption of alcohol at month 6 in the nalmefene group was reduced by 60% compared to 47% in the placebo group. The difference between nalmefene and placebo of about two heavy drinking days/month and 11 gm alcohol/day was clinically significant. Moreover, the benefits of reduction in alcohol consumption during treatment with

nalmefene were also seen in improvement in the CGI score (Clinical Global Impression), and a significant difference in indices of hepatic function (GGT and ALAT) compared to placebo. The use of nalmefene-as-needed constitutes a new pharmacological treatment both in terms of efficacy and personalization of therapy. It can be considered acceptable for patients that desire to reduce excessive consumption, but not complete abstinence.

Concerning psychotherapeutic treatment, it should be noted that monitoring the consumption of alcoholic beverages during prevention of recurrences allows the patient to use strategies and resources to affront the condition. The individual must be accompanied by comprehension of the mechanisms that lead to recurrence, and in particular to the recognition of high-risk situations [63].

A craving diary can be very useful, in which the patient is asked to note the level of desire for alcohol keeping in mind several factors: the moment in which the experience presents itself, when it goes away and the strategies used to deal with it.

The patient can be helped to confront craving using strategies that allow them to think of something else, in such a way that time passes, and the craving thereby decreases. Moreover, it is fundamental that the experience is shared with another person, accepting it and reflecting on the fact that it will have a resolution. For the patient, it is important to focus on the corporeality and describe the parts of the body in which the tension is felt. Several recent studies have shown the efficacy of meditation (mindfulness) as an anti-craving strategy and to prevent recurrence [63].

A third-generation cognitive-behavioural approach is the metacognitive therapy proposed by Wells [64]. The metacognitive model of pathological dependence (theory of intrusion elaborated by desire) [65] explains the maintenance of the disturbance on the basis of the following process: exposition to conditioned subthreshold stimuli associated with alcohol fuels the presence of intrusive thoughts and memories associated with alcohol abuse. These latter can be elaborated voluntarily. Such a voluntary process is oriented to prefigure images, information and memories relative to the experience of alcohol consumption is defined as a wishful thought. In the short term, the wishful thought helps to manage negative mental states, shifting attention and thoughts far away from this, and focusing on positive emotions and sensations connected with alcohol consumption. In the medium to long term, the wishful thought produces an escalation of craving if the desired object continues to be imagined but not obtained, and increases the possibility of increasing consumption.

Research [66] has shown that the wishful thought seems to have a role in the transition from excessive consumption to abuse, and may also be related to maintenance of the degree of severity of alcoholism. According to the metacognitive model, patients can benefit from learning how to recognize the activation of wishful thinking, how to control it and shift one's attention elsewhere. However, this approach appears to be indicated only for problematic drinkers, or for those with moderate alcohol abuse.

Conclusions

Disturbances correlated with the use of alcohol should be considered as a social and health emergency. Nonetheless, the available scientific evidence does not provide precise and identifiable limits over which ethanol-related damage occurs, although it is clear that there is a linear correlation between systematic exposition to alcohol and morbidity and mortality. In this regard, campaigns aimed at primary prevention should avoid using the term 'moderate alcohol consumption'. The concept of reduction versus abstinence has become useful in terms of clinical, social and economic considerations. The possibility of reducing risk and limit organ damage, the opportunity to involve the patient in a therapeutic course of modular treatment aimed at abstinence, the possibility of prevention to avoid evolution into more severe forms of alcoholism and the need to reduce the social and economic impact of alcohol are important goals that can be reached in view of all the therapeutic strategies taken into consideration. Reduction in alcohol consumption can be a valid intermediate objective from social and therapeutic standpoints, and is even acceptable for patients who are not able or who are poorly motivated towards abstinence in order to reduce the clinical risks related to consumption of high levels of alcohol. New pharmacological strategies can be helpful in achieving such a therapeutic objective. In particular, nalmefene, a modulator of the opioid system with antagonist activity on opioid mu and delta receptors and partial agonist activity on opioid kappa receptors, appears to be efficacious in reducing alcohol consumption.

Conflict of interest

Dr. Giuseppe Fertonani Affini received a "grant" to search for the article published. The amount received will be allocated for a scholarship aimed at research into alcohol-related problems.

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Enhancing stability in bipolar disorder

Il valore della stabilizzazione nel disturbo bipolare

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Summary

Objectives

Bipolar disorder (BD) is usually diagnosed after a delay of at least 10 years; during this period, bipolar subjects often take inappropriate treatments. The purpose of this overview of the current literature is to provide a specific point of view regarding several critical issues such as diagnosis, management and treatment of this complex illness.

Methods

A detailed search of the literature was conducted in Pubmed/Medline, Scopus, Science Direct, PsycLit and PsycInfo databases to identify all publications in English language from January 1980 to January 2013. The study used the following terms: "Stabilization" and "Management" and "Bipolar Disorder" OR "BD" and "acute treatment" and "maintenance treatment".

Results

Mood stabilizers are the first-line treatment during manic, hypomanic and mixed episodes of BD. Lithium still represents the gold standard among all the currently available treatments of BD. Most of the available evidence suggests that mood stabilizers are effective in the acute treatment, maintenance and prophylaxis of BD. Quetiapine is the only one among the available second-generation antipsychotics to have an indication in the acute depressive episodes of BD, whereas both quetiapine and lamotrogine are indicated for the prophylaxis of depressive bipolar episodes. These agents can be used as monotherapy but also, more frequently, in combination.

Conclusions

Treatment of BD should be focused on maintenance therapy through the use of mood stabilizers. Antidepressant drugs should be avoided due to the possible induction of rapid cycling and the long-term instability.

Key words

Bipolar disorder • Mood stability • Maintenance treatment • Antidepressant medications • Mood stabilizers

Introduction

Misdiagnosis in psychiatry is quite common, but it is also frequent to get unexpected findings using the available psychoactive treatments. None of the clinical histories of individuals with bipolar disorder (BD) may be considered similar to another, and each case must be considered a unique clinical experience.

In most cases, diagnosis of BD is performed with a mean delay of about 10 years, and during this period bipolar subjects usually take inappropriate treatments that are active on aspecific symptoms [1-3]. Specifically, over 60% of patients with BD reported having received at least 1-4 previous diagnoses: the diagnostic delay is more pronounced in women with BD type II than in men [2]. One of the most important reasons concerning the mean diagnostic delay in BD is typically related to the various clinical presentations of the disease[4] and, in particular, to the fact that only a part of the clinical history is referred by bipolar patients who frequently deny their illness.

More generally, affective disorders are associated with a higher risk of suicide compared to the general population [5-9], and suicide is widely recognized as one of the leading causes of death in patients with BD [10]. In fact, suicide rates in patients diagnosed with BD (especially with BD type I) or severe recurrent depression are at least 20 times higher than those in the general population, and substantially higher than those in other psychiatric disorders. In BD suicide risk is on average 390/100,000/year (0.39%/year), which is 28 times higher than that of the general population. It is important to highlight that the early and timely diagnosis is also associated with a lower prevalence of suicide attempts and a less severity of the illness [1].

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Depressed mood is, no doubt, one of the most frequent symptoms during depressive bipolar episodes, although insomnia/hypersomnia, anorexia/hyperphagia, slow-down/psychomotor agitation are also very common [11]. In addition, DSM-IV-TR includes in the same diagnostic category patients with very different clinical features such as those with mania or mixed states (characterized by the presence of both depressive and manic symptoms). Subjects with a mixed episode frequently show heterogeneous clinical features: Kraepelin identified, within what we currently mention as bipolar spectrum [12-13], the following opposite psychopathological states "pure mania" and "pure depression" as well as many clinical variants including agitated depression, mania with poverty ideation, manic stupor, depression with flight of ideas and inhibited mania [14].

The current diagnostic criteria also suggest the existence of a relevant heterogeneity within the different bipolar subtypes. The prevalence of mood disorders generally varies according to the different diagnostic criteria that were used. There is evidence that the same subject has a likelihood of 11.1% of receiving a diagnosis of BD according to DSM-IV-TR, 33.3% with Zurich "hard" criteria and 50% using Zurich "soft" criteria [15].

By using hyperactivity and duration of manic/hypomanic episode as criteria for the diagnostic evaluation, it is usually not possible to distinguish if patients with major depressive disorder have a bipolar or unipolar disorder. The present overview of the literature aimed to provide a critical and detailed point of view concerning several crucial issues such as diagnosis, management and treatment of bipolar illness, and to analyze the real value of stabilization in the long-term outcome of BD.

Methods

We conducted a detailed search of the current literature using Pubmed/Medline, Scopus, Science Direct, PsycLit and PsycInfo databases in order to identify all English-language full-text publications from January 1980 to January 2013.

The search used the following terms: "Stabilization" and "Management" and "Bipolar disorder" OR "BD" and "Acute treatment" and "Maintenance treatment". One researcher (GS) independently conducted the search, and any discrepancies regarding the inclusion of potentially eligible studies was performed by consulting the second senior author (PG).

The reference lists of all included studies were also manually consulted to include additional eligible studies. We included all English-language studies with original data about the main topic of the research. Approximately 150 studies were recognized as eligible, and 90 were included in this literature overview.

The use of antidepressants in the treatment of BD

To date, there is no study showing that antidepressant drugs add stabilizing effects to the long-term treatment of BD. According to the stress-diathesis model [16-18], we may imagine that BD is divided into 3 general stages. 1) An early phase that can be defined by the presence of a biological predisposition (vulnerability), which is necessary but not sufficient for the development of bipolar illness. The beginning of this phase is usually represented by the onset of a reactive depression; in these cases, if the subject is not treated with antidepressant drugs, only a cyclothymic disorder characterized by mood fluctuations without significant psychosocial impairment may emerge. 2) A hypomanic/manic-depression-free interval as a result of the worsening of any mood cycle that is characterized by pathological mood fluctuations (here, a psychiatric disorder is usually emerging). 3) A cycle of hypomanic/manic-depressive-free interval that has usually a negative outcome since it is characterized by higher clinical severity than other subtypes.

Importantly, it is more difficult to (retrospectively) evaluate euphoria rather than hyperactivity in clinical practice, and similarly the distinction between hypomania and mania is not always straightforward [19]. Clinicians should be able to diagnose BD even after depressive episodes, during hyperactivity: BD is a mood disorder that leads to several impairments in the biological rithms. When hypomania occurs, patients do not refer to psychiatrists for several reasons. Firstly, they do not realize the "fluctuations" of their mood (it is possible that symptoms such as delusions, hallucinations or impaired insight occurred). Second, our society tends to judge individuals based on their levels of performance, and hypomania is not generally considered pathological by most subjects. Hypomania or mania last few days and generally represent the egosyntonic part of the disease whereas depressive episodes usually represent the egodystonic part that was largely declared by patients, being experienced as painful and disabling. Moreover, studies clearly indicated that depression is a cyclic and also recurrent disease (consisting of phasic phenomena) [20-22]. If antidepressant medications that are usually associated with a reduction of the perceived depressive pain are prescribed, as mentioned, patients are forced to believe that antidepressant medications can really "heal", and that his/her psychiatrist was able to intervene in a very effective and timely manner, without considering that a new hypomanic/manic episode could be induced.

Antidepressant medications should be considered, in our opinion, as drugs with strong stimulant properties that may induce mood instability. These are molecules that act by reducing the free intervals of the illness up to determining their suppression over time: under antidepressants, the

disorder may acquire the specific features of continuous cyclicity [23-27]. Currently, there are no studies demonstrating that antidepressant drugs are actually useful in the treatment of BD, and some researchers [28-30] have suggested that this is related to the fact that most mood disorders diagnosed as "unipolar" are actually bipolar types.
Rapid cycling BD was, up to 30-40 years ago, a rather uncommon diagnostic subtype that was mainly observed as a long-term complication of BD. Rapid cycling BD seems to be increasing due to the fact that patients are currently much more sensitive to stimulants than in the past; patients continuously sought stimulants as a valid form of emotional support [25 31-33]. These are individuals having a strong tendency towards consumption of stimulants such as alcohol, caffeine and cocaine, and often exhibit altered behaviours determining insomnia, which enhances the tendency to mania. The use of stimulants causes the secretion of dopamine, catecholamines and endorphins [24-36] leading to increased resistance to fasting, a "doping" effect on the body and resulting in clinical hyperactivity and marked alteration of the sleep/wake and activity/rest biorhythms.
According to Koukopoulos and Ghaemi [20], the "primum movens" underlying mood disorders is mania. The treatment of BD cannot, therefore, be effective without treating manic episodes. Even in some depressive/mixed episodes, the key element of the illness is represented by mania because thoughts are accelerated, and there is a disabling hyperactivity in addition to motor slowing. Moreover, subjects with BD may have few thoughts, they do not want to do anything and they are agitated, but mania is usually present. The outcome of subjects suffering from BD is variable and largely depends on the episode for which bipolar individuals are treated. Whether a stabilizing treatment is prescribed in a timely manner (this should not include the use of antidepressant drugs), subjects can heal, and even interrupt pharmacotherapy for a long period of time. In most cases, however, people suffering from such diseases are forced to continue treatment due to the recurrence of the "self-doping" tendency and the frantic search of stimulants as a form of emotional support.
These are individuals with a chronic tendency to self-induce mania, they are generally depressed and have a tendency to fail in the achievement of long-term stability as they are biologically and psychologically dependent by the manic episode. To help these people heal, mania and hypomania must be adequately diagnosed even if diagnosis of the latter is very difficult being usually retrospective [19 37].
Overall, BD is a disease that severely impairs biorhythms and typically needs the use of mood stabilizers which, however, may exert different of effects depending on the episode for which bipolar patients were treated.

Currently available medications with mood stabilizing properties

Mood stabilizers are the first-line treatment during manic, hypomanic or mixed episodes of BD [38]. Most evidence suggests that mood stabilizers are effective both in the acute treatment of manic/hypomanic episodes as well as in the maintenance treatment focused on the prevention of relapses of BD [38-39]. To date, none of the second-generation antipsychotics has been recognized in the acute treatment of depressive episodes of BD with the exception of quetiapine [40].
Mood stabilizers can be used as monotherapy but also, more frequently, they may be combined in those illness subtypes that are characterized by elevated aggressiveness or impulsiveness. The association of a mood stabilizer with first- or second-generation antipsychotics is frequent and may offer some advantages particularly related to the lower latency of response [41] in the treatment of acute episodes.
The first-line treatment of BD is, undoubtedly, represented by lithium [41]. Being a drug with a low therapeutic index, lithium levels should be regularly checked in serum. The use of lithium requires special caution such as the frequent monitoring of renal, thyroid and cardiovascular functioning. When administered in the elderly, lithium may frequently induce accumulation associated with decreased renal clearance.
Lithium can also frequently cause tremor, nausea, vomiting, polyuria and polydipsia. Hyperreflexia, confusion, convulsions, tremor, dysarthria, profuse diarrhea, neurological signs and finally coma are clear signs of toxicity [42]. In case of serious contraindications related to the utilization of lithium (e.g. severe renal failure), the use of other mood stabilizers is highly recommended.
Sodium valproate is one of the most widely used drugs among all mood stabilizers: this medication, however, can often lead to weight gain, abnormal liver functioning, thrombocytopenia, gastrointestinal disorders, neurological disorders and sedation [43]. Carbamazepine should be prescribed with extreme caution due to the frequent interactions with other drugs and possible hepatotoxic effects [43].
Among all drugs which are commonly used to treat BD, antiepileptic drugs that have not yet been recognized as having mood stabilizing properties are also used. First, topiramate may induce adverse effects such as sedation, anorexia, nephrolithiasis, neurological and gastroenterological disorders; oxcarbazepine is associated with hyponatraemia to a greater degree than carbamazepine; lamotrigine is frequently associated with sedation, dizziness, neurological disorders (diplopia, ataxia, blurred vision), gastrointestinal disturbances (nausea and vomiting) and skin rash (Stevens Johnson Syndrome) [43].

In addition, atypical antipsychotics may be used in the treatment of BD: olanzapine, quetiapine, risperidone, paliperidone, aripiprazole, ziprasidone and asenapine [44-48]. However, based on the current literature, among all atypical antipsychotics, quetiapine is the only medication that is indicated in the treatment of depressive, manic and mixed episodes of BD. It therefore represents an effective pharmacological option in both the short- and long-term treatment of BD [49].

Quetiapine monotherapy and combination with additional mood stabilizers may be useful in the prophylaxis of depressive episodes [50]. All the most recent guidelines for the treatment of acute bipolar depression recommend quetiapine as a first-line option, and suggest that it may also be useful for continuation and maintenance treatment of BD [50-53]. The antidepressive effects of quetiapine in bipolar and unipolar depression with a special focus on its early onset of action and sleep improving effects have recently been reviewed by Rihmer [54].

In the context of BD, quetiapine has shown efficacy when used as monotherapy or adjunctive therapy for acute manic/mixed episodes in adults [55]. Maintenance treatment with quetiapine combined with lithium/divalproate significantly increased the time to recurrence of any event (mania, depression, or mixed episode) regardless of the polarity of the index episode compared with placebo and lithium/divalproate [56].

Atypical antipsychotics differ in terms of safety and tolerability. These drugs should be prescribed with caution in the elderly due to the increased susceptibility to adverse effects such as sedation, extrapyramidal and hypotension. In the elderly, it is also necessary to slowly increase the dose of atypical antipsychotics; the daily therapeutic dosages should be lower than in younger patients. They may also induce anticholinergic and extrapyramidal adverse effects.

Quetiapine is usually, considered a safe medication; it may be transiently associated with sedation and hypotension particularly in the early phases of treatment [49]. The most common adverse effects that may be induced by other atypical antipsychotics are: hyperprolactinaemia with risperidone; leukopenia and agranulocytosis, seizures, tachycardia, orthostatic hypotension, myocarditis, increased risk of pulmonary embolism and severe constipation with clozapine; weight gain and metabolic syndrome, sedation and orthostatic hypotension with olanzapine; lengthening of the QTc interval and eventual induction of arrhythmias with ziprasidone; headache, insomnia, dyspepsia, nausea, vomiting and constipation associated with the use of aripiprazole; sedation, akathisia and oral hypoesthesia with asenapine [44 45].

There are also some medications that have demonstrated promising properties in the treatment of BD: allopurinol (600 mg per day) [57], memantine (10-30 mg per day) [58], tamoxifen (80 mg per day) [59-61] in manic episodes; modafinil (200 mg per day) [62], N-acetylcysteine (2000 mg per day) [63 64], pramipexole (1-2.5 mg per day) [65 66], riluzole (50-200 mg per day) [67 68] in depressive episodes; memantine (10-30 mg per day) [58] in mixed episodes. Tables I and II summarized the most important clinical characteristics of medications with mood stabilizer properties.

Management of BD using mood stabilizers

The discovery of mood stabilizers occurred for "serendipity" [69 70]. Mood stabilizers may be defined as those drugs that are active in the treatment of mood episodes as well as in the prevention of bipolar reoccurrences enhancing stability over time. Since 1949 when John Cade published his article "Lithium in the treatment of psychotic agitation" [71], lithium has never ceased to be used in psychiatry. The Australian researcher had suggested the lethargy that lithium may induce in rodents, and he had administered lithium to patients with a history of manic disorder obtaining successful results.

However, in the late 1940s, lithium was also used as sodium chloride in patients with cardiovascular disorders leading to cases of severe poisoning and death. These deaths postponed for more than 20 years the clinical use of lithium for the treatment of mania. Only at the end of 1960, after a series of controlled clinical studies focused on the efficacy and tolerability of this drug, lithium was regularly introduced by Gershon [72 73] in the United States as a short-term treatment and prophylaxis of BD.

In addition, the clinical use of certain drugs mainly used as antiepileptic medications (carbamazepine, oxcarbazepine, sodium valproate, lamotrigine, gabapentin, topiramate) significantly contributed to the pharmacotherapy of major psychopathological disorders, and in particular, of those included within the affective spectrum.

Drugs with mood stabilizing properties can be divided into the following categories: 1) dibenzodiazepines, 2) atypical antipsychotics, 3) antiepileptic drugs, 4) lithium.

One of the most important failures in the history of psychiatry occurred when it has been postulated that BD was the sum of two diseases: mania that may be successfully treated with anti-manic drugs and depression that may be successfully treated with antidepressant medications; this assumption largely contributed to suicidality among patients with BD.

The indiscriminate use of psychoactive compounds having antidepressant properties in subjects with BD increased, in our opinion, the instability over time, and the global severity of the illness. During the last centuries, some prejudices concerning the uncertain tolerability and inadequate efficacy of mood-stabilizing drugs have limited the use of these compounds. Negative attitudes include painting all mental patients as incompetent and

TABELLA I.
Major currently available mood stabilizing medications. *Principali farmaci stabilizzanti del tono dell'umore attualmente in commercio.*

Drug	Main clinical uses	Pharmacokinetics	Mechanism of action
Lithium	Short and long-term prophylactic treatment of BD I	Peak concentration after 1-1.5 hours; lithium does not bind to plasma proteins and is excreted by the kidney; half-life 19-24 hours	Currently unknown; presumable block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Carbamazepine	Treatment of acute mania and prophylactic treatment of BD I; treatment of epilepsy	Limited water solubility; active metabolites through the system oxidative hepatic; slow absorption; half-life 12-17 hours; self-induction of its own metabolism	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Sodium valproate	Treatment of acute mania and prophylactic treatment of BD I; treatment of epilepsy	Half-life 5-20 hours; 70-95% plasma protein binding	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Oxcarbazepine	Treatment of epilepsy	High lipophilicity, volume of distribution of 49 L, serum protein binding 40%	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Lamotrigine	Prophylaxis of depressive relapses in bipolar depression; treatment of epilepsy	Bioavailability 98%, peak plasmatic levels 1-3 hours, half-life 33 hours; binding serum protein: 55%	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Gabapentin	Treatment of epilepsy	Bioavailability 60%; peak plasmatic levels 2-3 hours; it does not bind to plasma proteins; volume of distribution: 58 L; half-life 5-7 hours	Block of the voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate
Topiramate	Treatment of epilepsy	Bioavailability 81%; peak plasmatic levels 2-3 hours; half-life 21 hours; 13-17% is bound to plasma proteins; 81% eliminated through the kidney	Block of voltage-dependent sodium channels with stabilization of neuronal membranes and consequent release of neuronal glutamate

Main adverse effects	Dosage	Plasma levels	Recommendations
Weight gain, polyuria, polydipsia, tremor, hypothyroidism, flattening-T-wave inversion, motor incoordination, weakness, seizures, peripheral neuropathy, benign intracranial hypertension, diarrhoea, nausea, decreased appetite, alopecia, acne, psoriasis	900-1200 mg	0.4-1 mEq/l	The onset and severity of side effects are generally related to plasma levels. The determination of lithium in the serum should be carried out once a week for 1-2 months, once a month for 6-8 months and every 2-3 months later
Hyponatraemia, elevated liver enzymes, liver toxicity, blurred vision, diplopia, ataxia, dizziness, motor incoordination, confusion, rash, leukopenia, aplastic anemia, Stevens-Johnson syndrome, pancreatitis, conduction disturbances	800-1600 mg/ day	-12 mg/ml	Absolute contraindications to the use: blood disorders by bone marrow suppression, narrow-angle glaucoma, first trimester pregnancy, concomitant clozapine administration
Weight gain, increased liver enzymes, reversible thrombocytopenia, epistaxis, bruising, nausea, vomiting, anorexia and dyspepsia, ataxia, dysarthria, tremor, leukopenia, altered cognitive functioning, encephalopathy and hemorrhagic pancreatitis	1200-1500 mg/ day	50-100 µg/ml	In the elderly, the free fraction of the drug may increase up to 70%. Elevated free fraction of the drug (about two times higher) in diabetes mellitus and renal failure may be found
Skin eruptions (Stevens-Johnson), asthenia, dizziness, memory impairment, headache, tremors, sleep disorders, numbness, affective lability, tinnitus, ataxia, depression, diplopia, anxiety, weight loss, postural hypotension	600-1200 mg/ die (max 3000 mg/day)	0-4 µg/ml	Monitor patients with frequent visits. In case of overdose, possible cardiac conduction disorders, respiratory and electrolyte abnormalities
Rash (Stevens-Johnson syndrome, Lyell's syndrome), fever, arthralgia, lymphadenopathy, eosinophilia, teratogenicity. Because of possible cross-reactions, it should be given with caution in patients with known hypersensitivity to carbamazepine and phenytoin	50-200 mg	3-14 mg/L	Monitor patients with frequent visits. Carbamazepine reduces the time of elimination of lamotrigine by 50% (14 hours) whereas sodium valproate, by inhibiting its metabolism, increases its half-life to 70 hours
Cases of suicidal ideation and suicidal behavior. Drowsiness, dizziness, fatigue, ataxia, tremors, palpitations, hypertension, skin rashes (Stevens-Johnson), leukopenia, impotence, increased liver enzymes, nausea, vomiting, diarrhoea, anorexia, joint pain, diplopia, ear infections, dizziness	900-1800 mg/ day (max 3600 mg/day)	4.5-5 µg /ml	Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, childhood
Nasopharyngitis, anaemia, anorexia, altered cognitive functioning, blurred vision, diplopia, visual disturbances, dizziness, tinnitus, ear pain, dyspnea, epistaxis, vomiting, constipation, upper abdominal pain, dyspepsia, abdominal pain, alopecia, rash, pruritus, arthralgia, nephrolithiasis	100-200 mg/ day	3-20 µg/ml	Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, children. It inhibits CYP2C19 (may interfere with the metabolism of diazepam, imipramine, moclobemide, proguanil, omeprazole)

TABELLA II.
Major atypical antipsychotic drugs that may be used in management of BD. *Principali farmaci antipsicotici atipici che possono*

Drug	Main clinical uses	Pharmacokinetics	Mechanism of action
Risperidone	Treatment of acute mania	Peak plasmatic levels 1-2 hours; 70% bioavailability, plasma protein binding 90%; half-life of about 20 hours, renal elimination	Activity on the following receptor systems: $5HT_2$, D_2, $alpha_1$ and $alpha_2$, H_1. 5H- risperidone is the active metabolite of the drug
Quetiapine	Treatment of acute mania and acute bipolar depression; prophylactic treatment of BD	Binding of quetiapine to plasmatic proteins is approximately 83%; half-life 7-12 hours	Activity on the following receptor systems: D_1, D_2, $5HT_2$. Norquetiapine, the active metabolite, has a high affinity for the norepinephrine transporter, histaminergic, $alpha_1$ and $alpha_2$ adrenergic, serotonergic $5HT_{1A}$ receptors
Olanzapine	Treatment of acute mania and prevention of relapse of manic episodes in BD	Peak plasmatic levels 5-8 hours; linear pharmacokinetics, bioavailability not affected by food intake; half-life 10-16 hours	Activity on the following receptor systems: D_1, D_2, D_4, $5HT_{2A}$, $5HT_{2C}$, $5HT_3$, M_1, $alpha_1$, H_1
Aripiprazole	Treatment of acute mania and prevention of relapse of manic episodes in BD	Peak plasmatic levels 3-5 hours; bioavailability 87%; plasmatic protein binding by more than 99% half-life 75-146 hours (depending on the activity of CYP2D6)	Activity on the following receptor systems: D_2, D_3, D_4, $5HT_{1A}$, 5HT2A, $5HT_{2C}$, $5HT_7$, $alpha_1$, adrenergic and H_1
Ziprasidone	Treatment of acute mania	Peak plasmatic levels 6-8 hours; bioavailability 60%; plasmatic protein binding of more than 99%; half-life 6.6 hours	Activity on the following receptor systems: D_2, $5HT_{2A}$, $5HT_{2C}$, $5HT_{1D}$, $5HT_{1A}$, H_1, $alpha_1$, M_1
Asenapine	Treatment of acute mania	Peak plasmatic concentrations within 0.5 to 1.5 hours; bioavailability 35%; plasma protein binding 95%; half-life 24 hours	Activity on the following receptor systems: D_2, $5HT_{2A}$, $5HT_{1A}$, $5HT_{1B}$, $5HT_{2C}$, $5HT_6$, $5HT_7$, D_3 and $alpha_2$

essere attualmente utilizzati nella gestione del BD.

Main adverse effects	Dosage	Recommendations
Anxiety, insomnia, agitation, headache, tachycardia, rhinitis, rash, drowsiness, fatigue, difficulty concentrating, dizziness, nausea, vomiting, abdominal pain, constipation, urinary incontinence, blurred vision, as well as sexual dysfunction, orthostatic hypotension, hyperprolactinaemia, hyperglycaemia, orthostatic hypotension, palpitations, weight gain, decreased libido and erection difficulties, tremor, rigidity, bradykinesia, malignant syndrome, thrombocytopenic purpura and priapism	4-6 mg die (max 16 mg day)	It should be administered with caution in patients with cardiovascular diseases. The association with phenytoin or SSRIs can cause extrapyramidal effects. The association with opioids can cause abstinence related to opioid withdrawal. The association with clozapine increases plasma concentrations. It may antagonize the effect of levodopa and other dopamine agonist agents
Leukopenia, hyperprolactinaemia, decreased free and total T4 and T3, increased TSH, nightmares, dizziness, drowsiness, headache, tachycardia, palpitations, blurred vision, orthostatic hypotension, rhinitis, dyspnoea, metabolic syndrome	25-800 mg die (max 1500 day)	Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, childhood
Drowsiness and weight gain, dry mouth, confusion, sedation, insomnia, orthostatic hypotension, tardive dyskinesia, neuroleptic malignant syndrome, diabetes and diabetic ketoacidosis with acute onset, increased levels of triglycerides and metabolic syndrome	2.5-20 mg die (max 30 mg day)	Use caution in patients receiving drugs that can cause depression of the central nervous system. Smoking and carbamazepine may lead to a reduction of concentrations. Fluvoxamine inhibits the metabolism of olanzapine. It may antagonize the effects of direct and indirect dopamine agonists
Headache, dyspepsia, vomiting, nausea, constipation, salivary hypersecretion, feeling light-headed or empty, insomnia or drowsiness, restlessness, blurred vision, fever, sweating, dysregulation of blood pressure and heart rate, muscle aches, allergic reactions, extrapyramidal symptoms, akathisia, tremor	2.5-30 mg day	The co-administration with CYP3A4 inhibitors of P450 enzymes, such as ketoconazole and erythromycin increases serum concentrations. Quinidine increases aripiprazole levels but reduces those of its metabolite, dehydro-aripiprazole. Carbamazepine reduces the levels of both medications. Valproate reduces serum levels of aripiprazole by 25%. The co-administration of lamotrigine may increase the risk of Stevens-Johnson syndrome
Restlessness, dystonia, akathisia, extrapyramidal disorders, parkinsonism (including cogwheel rigidity, bradykinesia, hypokinesia), tremor, dizziness, sedation, drowsiness, headache, blurred vision, nausea, vomiting, constipation, dyspepsia, dry mouth, salivary hypersecretion, musculoskeletal stiffness, weakness, fatigue	80-160 mg day	Monitor patients with frequent visits. It can induce QT prolongation. Contraindications: hypersensitivity, lactation, children
Hyperglycaemia, elevated levels of total cholesterol, triglycerides, significant prolongation of the QTc interval, somnolence, akathisia and oral hypoaesthesia, weight gain and appetite, dystonia, akathisia, dyskinesia, parkinsonism, sedation, dizziness, dysgeusia, increased liver enzymes, muscle stiffness, fatigue	5-20 mg day	Not approved in the elderly, dementia-related psychosis for the higher risk of death. Monitor patients with frequent visits. Contraindications: hypersensitivity, lactation, childhood

incurable; as a result, even though effective pharmacological medications are currently available, most patients neither seek nor receive appropriate treatments.
BD is usually a disease with a duration of at least two years, and the treatment with mood stabilizers must take into account a sufficient period of treatment of at least two years at adequate dosages [4]. The characteristics of mood stabilizers should be: absence of depressive effects and efficacy on manic symptoms, good safety and tolerability, thus allowing a good adaptation among bipolar subjects [4 72 73]. The aim of mood stabilizers is also to restore biorhythms [74-77].
Lithium is, no doubt, widely recognized by several guidelines as the gold standard for the treatment of both acute episodes as well as maintenance therapy of BD [52 78]. In Italy, in contrast to other countries, the slow-release lithium formulation is not available. This formulation is clinically associated with lower dropout rates than the quick-release lithium (although there are not currently, to our knowledge, controlled studies that compare the long-term outcome of patients using these different formulations) probably due to the possible induction of a kidney damage related to the quick-release of lithium. The quick-release of lithium is also able to overcome the threshold of renal re-absorption; it may not adequately act during the entire duration of a manic episode.
These manic episodes usually occur, in our experience, in the late afternoon or in the early evening, when fatigue appears as dysphoria, and usually occurs together with the need to perform an appropriate response to environmental stressors and recall residual resources. Mood stabilizers must be able, as mentioned, to restore the sleep-wake biorhythm [69 79]. Sleep is, among all biological functions, one of the most fascinating and embarrassing mysteries in the field of neuroscience [80-82]. It is not only a quantitative phenomenon as sleep essentially plays the function of "anti-stress", able to antagonize the negative effects of the free radicals that have been accumulated throughout the day. At a molecular level, the effects of stress on neurons are clearly evident at the end of a manic episode. Neurons remain without tigroid substance, appear as hypotrophic and have few dendritic arborizations and/or connections with other neurons [83 84].
Sleep would be the price that individuals have to pay to allow the daily neuroplasticity and neurogenesis processes [81]. The most useful hours of sleep are those ranging from the sunset to those immediately following the midnight: sleep at this stage largely depends by the release of cortisol [85]. Mood stabilizers should be able to restore these useful (crucial) hours of sleep; depressed subjects usually feel better in the evening, but this often coincides with the onset of hypomania (not adequately reported by patients). When subjects perceive a state of well-being, they really experience a moment of discomfort and should be treated with reasonable dosages of mood stabilizers [86]. Mood stabilizers should also be able to restore a reliable activity/rest biorhythm, in particular for what concerns the most significant life activities of subjects, such as occupational functioning. Mood stabilizers should be able to restore biorhythms that patients are not be able to restore, thereby giving subjects a new type of balance [69 79].
Another critical aspect must be mentioned. BD is frequently associated with high mortality rates as it is associated with a high rate of metabolic syndrome: it may be clearly defined as "the disease of exaggeration". BD is associated with many cardiovascular disorders such as arterial hypertension and heart failure. Whenever insomnia, abnormal activity/rest rhythm, metabolic syndrome and medical diseases occur, clinicians have to consider the diagnosis of bipolar illness, and therefore adequately treat patients taking into account the existence of comorbidities.
Although lithium represents, as mentioned, the gold standard in the treatment of BD [4], there are limitations in the prescription of this medication as monotherapy especially in terms of tolerability and uncertain compliance (lithium should never be interrupted even after a long-term period). Moreover, it should be not rapidly discontinued due to the increased risk of suicide [87 89] and the rebound of mania/hypomania that can be induced with rapid discontinuation [89 90].
Mania/hypomania induced by the rapid interruption of lithium can last up to 18 months and may be dramatically characterized by an increased risk of suicide [87 88 91]. Whether clinical conditions do not allow the administration of lithium or there are serious issues concerning the utilization of lithium, mood stabilizers as similar as possible to lithium should be administered.
Nonetheless, the perfect mood stabilizer does not exist. Mood stabilizers should: 1) exert anti-manic properties and should not induce depression, 2) have not antipsychotic properties (especially with high-affinity for D_2 receptors), 3) be medications that do not block the transport of catecholamines, 4) be associated with a good clinical profile in terms of safety and tolerability; 5) be associated with a good compliance; 6) be able to act as long-term agents associated with stable plasma levels (and thus it would be preferable to use slow-release formulations).

The importance of stability: conclusive remarks

The best treatment of BD is maintenance and continuation therapy, that should not include antidepressant or anti-manic medications that tend to act according to a cross-sectional limited perspective [92 93]. However, most

subjects with BD are examined during the acute manic or depressive episodes, and diagnosed as having of psychosis/schizophrenia or major depression; therefore they are treated with high-dosages antipsychotics or antidepressants, respectively, according to an approach focused on crisis intervention.

If antipsychotics (especially those with high-affinity for D_2 receptors) were used, considering the cyclical nature of the disorder, they can lead to depression that will be treated using antidepressant medications. Conversely, if antidepressants were used, they may induce mania/hypomania and subsequently, over time, long-term instability and rapid cycling forms [94]. In order to enhance stability in BD, it is necessary to emphasize long-term strategies and highlight the relevance of a terminological mistake that has been proposed for a long time: the care of BD should not be based on the use of those drugs having "anti-" properties (anti-manic, anti-depressant), but upon the use of "pro-" strategies (pro-health, pro-brain function, etc.).

A typical manic-depressive cycle usually includes the following pattern: mania/hypomania-depression-free interval and, more occasionally, the alternative pattern mania/hypomania-depression-free interval. This latter alternative cycle of BD is usually associated with a lower response to treatment and less favourable outcome than other subtypes [95]; in addition, this cycle is clinically prevalent when mania/hypomania is not appropriately diagnosed [19 37]. Clinicians need to be completely aware of the increased severity associated with this illness cycle compared to others.

The most useful treatments of BD are also those that tend to not impair insight/awareness into illness as well as the proper activation of the frontal and prefrontal brain areas. BD requires adherence to treatment since subjects must be able to realize the implications related to the illness according to the use of psycho-educational strategies [96].

Finally, in order to correctly restore individual lifestyles as well as to promote a rehabilitative perspective, it is necessary to promote the most adequate care focused on socio-cultural integration. This cannot ignore patients' motivation to care that can be enhanced through the use of mood-stabilizing medications able to satisfy the following characteristics: efficacy, safety and tolerability, and should not result in significant life changes (that can be perceived as invasive by patients).

Such medications should be dimensionally designed to control emotional reactivity together with restoring biorhythms. Historically, the first treatment in BD were: lithium and haloperidol; lithium and antiepileptics; lithium, antiepileptic drugs and second-generation antipsychotics. Quetiapine is currently, among all atypical antipsychotic drugs, a good option in the treatment of depressive, manic and mixed episodes of bipolar illness. Considering its early onset of action and its ability to stabilize the biorhythm awake/asleep, quetiapine represents an interesting therapeutic option in BD [97 98]. However, the current scenario of mood stabilizing agents may provide alternative or adjunctive strategies to strongly improve the quality of life of patients suffering from BD.

Conflict of interest

Prof. Girardi has served as a consultant to, or has engaged in research collaborations Organon, Eli Lilly, Janssen, Merck, Bristol-Myers Squibb, Pfizer, AstraZeneca Corporations e Innova Pharma. Dr Serafini has served as a consultant to, or engaged in research collaborations with Bristol-Myers Squibb, Janssen-Cilag, Eli Lilly, Glaxo Smith Kline and AstraZeneca, Innova Pharma, Lundbeck, Servier.

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