Dual diagnosis: an intriguing and actual nosographic issue too long neglected

Doppia diagnosi: complessità nosografica e attualità di un "terreno di confine" a lungo emarginato

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SUMMARY. **Background.** The term "dual diagnosis" (DD) has been used in clinical practice for years. However, there is confusion about these medical cases, which consist in the presence of both a psychiatric disorder and a substance abuse disorder (in this case, alcohol). There are evidences that in the alcohol use disorder (AUD) population, 50.3% of patients had a psychiatric comorbidity during their lifetime. Nevertheless, to these days there are not any thorough guidelines for the management of these patients. A precise nosography would prevent delay in diagnosis and treatment and all the self-evident negative outcomes of those delays. **Materials and methods.** A literature search was performed in PubMed, Web of Science, and Scopus, including studies published between 1980 and 2015. Search terms were: "guidelines", "treatment", "comorbidity", "substance abuse", "alcohol", "dual-diagnosis", "etiopathogenesis", "outpatient", "inpatient", "unit", "diagnosis". Out of 1045 titles, 43 studies were included in this article for their relevance on definition and nosography of DD. **Results.** Taking into account the state of art available in the literature, we contributed to clarify the definition of DD in the alcohol addiction field. Clinical data confirm high prevalence of DD, and allow to better describe and understand the complex relationship between alcohol dependence and other psychiatric diseases. **Conclusions.** We believe that a clear nosographic framework and a precise diagnostic process are essential for a timely management of every case, using specific guidelines to standardize and improve clinical practice. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which introduces dimensional approach, could be a useful tool to improve diagnostic accuracy.

KEY WORDS: dual diagnosis, alcohol dependence, nosography, epidemiology, guidelines, etiopathogenesis.

RIASSUNTO. Il termine "doppia diagnosi" è entrato da anni a far parte del lessico clinico ma la complessità riguardo questi quadri clinici caratterizzati dalla compresenza di un disturbo psichiatrico e di un disturbo da uso di sostanze (nel nostro caso, da alcol) è ancora molta. Nonostante sia dimostrato che nella sola popolazione affetta da abuso di alcol (DUA) il 50,3% dei soggetti abbia avuto un concomitante disturbo psichiatrico nell'arco di vita, a oggi non vi sono linee-guida esaustive per la gestione di questi casi. Difatti, l'incertezza nosografica non può che tradursi anche in un ritardo diagnostico e di cura, con evidenti effetti negativi per la salute dei pazienti. **Materiali e metodi.** È stata effettuata una ricerca sistematica della letteratura sui principali motori di ricerca quali PubMed, Web of Science e Scopus. Sono stati presi in considerazione articoli pubblicati dal 1980, anno di pubblicazione del DSM-III, al 2015. I termini di ricerca sono stati: "guidelines", "treatment", "comorbidity", "substance abuse", "alcohol", "dual-diagnosis", "etiopathogenesis", "outpatient", "inpatient", "unit", "diagnosis". Dei 1045 articoli emersi, 43 sono stati inclusi in questo articolo per la loro rilevanza sulla definizione teorica e sulla nosografia della doppia diagnosi. **Risultati.** A partire dai dati disponibili in letteratura abbiamo dato conto della ingente rilevanza epidemiologica del fenomeno e abbiamo illustrato i principali contributi nosografici disponibili in merito. **Conclusioni.** Alla fine della rassegna proponiamo in dettaglio il contributo offerto dal DSM-5, ritenendo che le peculiarità di questa proposta nosografica, dai non irrilevanti connotati dimensionali, possa essere utile per una migliore e più efficace descrizione/gestione del fenomeno, premessa indispensabile per approntare strategie terapeutiche più adeguate ed efficaci.

PAROLE CHIAVE: doppia diagnosi, alcolismo, nosografia, epidemiologia, eziopatogenesi, linee-guida.

INTRODUCTION

Dual diagnosis (DD) is defined by the World Health Organization (WHO) as «the coexistence of psychoactive substance use and another psychiatric disorder in the same person»[1]. According to the United Nations Office on Drugs and Crime (UNODC), DD is a term used to describe a «subject diagnosed with a problem of alcohol or drug abuse in addi-

tion to other commonly-occurring psychiatric or depressive disorders or schizophrenia»[2]. DD is the coexistence in the same subject of two or more psychiatric disorders, one of which is the "pathological intake" of psychoactive substances.

Because of considered a "border territory" among different field of medicine, such as psychiatry, toxicology, gastroenterology, and internal medicine, DD has not received an adequate attention in terms of nosographic-diagnostic overview and therapeutic strategies. The epidemiological available data in the literature, however, suggest that this is not a "marginal" clinical issue. Nora D. Volkow, Director of the National Institute on Drug Abuse, states that «according to epidemiological studies, 6 of 10 people abusing of alcohol and drugs have also a mental disorder, and 25 to 60% of people with a mental disorder have also substances addiction»[3]. This critical issue can only challenge clinicians and researchers to the search and find an adequate nosographic framework and treatment to this phenomenon. DD includes, in real world, a broad and diversified spectrum of clinical pictures: a primary mental disorder which causes the increase of substance intake and the possible development of an addiction; a substance abuse and/or withdrawal leading to a psychiatric symptomatology; the reversible/temporary worsening of a psychiatric condition due to the substance intake; the coexistence, independently developed, of substance abuse and mental disorder. Additionally, DD is a critical issue for job seekers because the patients often have a strongly compromised socio-economic functioning with important difficulties in socio-relational and economic field (family, work, etc.), and also different and important organ damages[4]. Despite the apparent epidemiological impact of the issue and its clinical research relevance, the concept of DD remains a complex, sometimes elusive clinical reality, with often uncertain nosographic borders. This is partly determined by the common consideration that substance addiction is an independent phenomenon, separated from the psychopathological field. Such factitious dichotomy reflects the lack of a common epistemological framework and the consequent difficulties in the use of nosographic criteria. This leads to inaccuracies and delays in the diagnostic process and in the definition of a therapeutic design.

The aim of this review is to provide an overview of the DD disorder, including epidemiological data and the various theoretical contributions, taking into account the latest classification hypotheses, their specific features and benefits. Our study will pay attention, among the various psychoactive substances, to alcohol.

MATERIALS AND METHODS

A systematic literature search was conducted in PubMed, Web of Science, and Scopus databases. Articles that have been published from 1980, the year of publication of DSM-III, until the 2015 were considered. The search terms were: "guidelines", "treatment", "comorbidity", "substance abuse", "alcohol", "dual-diagnosis", "etiopathogenesis", "outpatient", "inpatient", "unit", "diagnosis". Other articles have been selected for their relevance by the authors from the bibliography of articles previously chosed.

Of the 1045 works emerged, 43 were included in this article for their relevance. In particular, large-scale epidemiological articles were taken into account to extrapolate data about the DD impact on the general population, theoretical articles to support a wider debate about the etiology of the question, and nosographic works to retrace the classification attempts among DD field made since the early 1990s.

RESULTS

Dual diagnosis epidemiological relevance

The Epidemiologic Catchment Area Survey (ECA) was realized involving more than 20,000 patients, recruited at home and in health centers, evaluated for possible psychiatric disorders through the Structured Clinical Interview of DSM (SCID)[6]. The results reported that nearly 30% of patients with psychiatric diagnosis suffered during their life also of drug addiction, conversely more than 50% of patients with addiction or substance abuse also developed a psychiatric disorder during their live. Specifically, 48% of schizophrenic subjects and 55% of patients diagnosed with bipolar disorder developed a substance addiction at a given time of their life. The percentage reaches 90% in patients with personality disorder[7].

Another large-scale epidemiological study, the International Consortium in Psychiatric Epidemiology, examined nearly 30,000 subjects from seven different countries: USA, Canada, Mexico, Brazil, Germany, the Netherlands and Turkey. About 35% of patients with substance addiction also received a diagnosis of affective disorder, 45% of anxiety disorder, and about 50% of personality disorder[8].

It has been observed that in alcohol use disorder (AUD) population, 50.3% of subjects had concomitant psychiatric disorders over the lifetime. Personality disorders were the most common (24%), followed by mood (16.8%), psychotic (8.3%), and anxiety (6.6%) disorders. In addition, the time order in which the disorder occurred was analyzed: results showed that the risk of developing AUD in patients with a prior psychiatric disorder diagnosis was lower compared to the risk of developing a psychiatric disorder in AUD patients, especially with regard to personality disorders[9].

These data are in line with other studies in the literature: for example, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)[10] shows a general, significant and positive association between psychiatric disorders and alcohol abuse or addiction; Farrell et al.[11] suggested how the prevalence of at least one psychiatric disorder significantly differed between alcohol dependent patients (29.6%) and the non-dependent population (12.2%).

From these data it is simple to understand how DD is a phenomenon of great epidemiological impact known in epidemiological studies for over 25 years. In addition, the understanding of the relationship between substance addiction and concomitant psychiatric disorder is the clinical focus for an effective and specific diagnostic definition, a prerequisite for developing an appropriate therapeutic strategy[12,13].

Dual diagnosis: definitions, nosographic contributions and etiologic theories

Despite the complex and "well known" relationship-interaction between the acute and chronic psychoactive substance intake and the presence of changes in psychic domains does not exist a unique nosographic framework describing these phenomena. In particular, in clinical practice, there is not a homogeneous and shared classification criteria for DD.

An attempt of classification was proposed in 1993 by First and Gladis[14]; they identified three classes of patients:

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- patients with primary psychiatric disorders and secondary dependence;
- patients with primary drug dependence and secondary psychiatric disorders;
- patients with independent psychiatric and dependence disorders.

The first group includes subjects in which the clinical evidence of the psychopathological disorder started before the use of drugs. The way the substance is used should also be related to the subject's personality and temperament: in fact, the substance in these subjects would perform as a presumed "self-healing" role, and its mechanism of action should carry to a partial attenuation of psychopathological symptoms. In these patients, the persistence of psychopathological symptoms have to be demonstrated also when the subject is not taking the substance.

The second group includes subjects with an episodic of psychiatric symptoms linked to the substance intoxication and/or withdrawal. In this case a temporal relationship between the drug intake or suspension and the appearance of the psychopathological symptoms must be demonstrated. The symptoms will be compatible with the type of substance taken. In this class are included also subjects with mental disorders related to chronic state of intoxication.

In the third group, the two disorders are independent, and the typology and severity of the psychiatric symptoms do not influence the addiction trend.

De Leon[15] divided the patient of residential communities into three groups:

- psychiatric patients with substance abuse/addiction (MICA: Mental Ill Chemical Abuser);
- patients with primary problems of drug addiction and severe psychiatric disorders (CAMI: Chemical Abusers With Mental Illness);
- patients with primary problems of drug addiction associated with personality disorders and/or psychiatric disorders (chemical abusers - CA).

Salomon's studies[16] partially resumed the First and Gladis classification, underlining the importance of an accurate parallel history: in type 1 patients, the diagnosis of primary psychiatric disorders should be laid only after an adequate time since the drug intake interruption. In this manner, the effects of withdrawal syndrome are not confused with primary psychopathological symptoms.

The most common etiological theories in the literature proposed to explain the strong prevalence of substance use disorder (SUD) in patients with psychiatric disorders, especially with schizophrenia and bipolar disorder, are the following:

- the most widespread theory is the Self-Medication Hypothesis (SMH), initially proposed for alcohol dependence. According to this theory, patients with mental health disorders would be more prone to stressful/dysphoric experiences. Such experiences also make them more prone to psychoactive substance intake to alleviate their condition. The substance would then be used to "take care of" anxiety/distress, or to compensate feelings of emptiness and apathy. For this reason, the drug would not be randomly chosen, but would be selected among others for its

"pharmacodynamic properties". For example, in mood disorders «hypnotic sedatives, including alcohol, allow to experience affection, aggression and proximity in individuals who otherwise would be cut off from emotions and relationships»[17]. Recently, SMH has been questioned because of lack of solid scientific evidence in literature[18-20];

- according to the Multiple Risk Factors Theory[21] in patients with mental disorders, the use of the drug, would be also favored by other risk factors (e.g., social isolation, poverty, lack of daily rehabilitation facilities, a history of traumatic events) that would all contribute to SUD development;
- finally, supersensitivity theory[22] postulates that a psychobiological vulnerability, determined by a combination between genetic factors and premature environmental events (e.g. perinatal), could interact with environmental stressors accelerating/precipitating/unmasking the psychiatric disorder manifestation and SUD.

It is important to emphasize that these theories could play synergistically and with different weight to illuminate the search for etiopathogenetic determinants of DD in the clinical history of each patient.

The nosographic contributions of DSM and ICD

The Diagnostic and Statistical Manual of mental disorders (DSM), published by the American Psychiatric Associaton (APA), reached its fifth edition in 2013, and it is a symptom-behavior-oriented, nosographic-descriptive tool that classifies symptomatic psychopathological manifestations and people's pathologic behaviors. Specifically, DSM describes, under a statistical-epidemiological point of view, the clinical manifestations of one or more disorders, regardless of their etiology, as a cluster of symptoms and or signs. The diagnosis requires that not all of the listed criteria are present, but only a predetermined number of them. In addition, for each disorder, DSM provides a label for comparison with ICD codes, the International Classification of Diseases and Related Problems, issued by the World Health Organization (WHO). Since the first DSM edition in 1951, the drug abuse diagnosis has undergone radical changes. In DSM-I, "addiction" was categorized into personality disorders[23]. The emphasis was given to the close association between toxic behavior and the "antisocial personality"[24]. Alcohol was the only abused substance considered in the diagnostic category. In DSM-II there was a specific section dedicated to "personality disorders and other non-psychotic disorders", which included drug addiction and a separated category for alcohol[25]. Diagnosis required the "evidence of habitual use or a clear need for the substance", but the presence of withdrawal symptoms was not the only gold standard for addiction diagnosis. Cocaine, for example, was described as a substance that did not cause withdrawal symptoms. In 1980, DSM-III considered drug use disorders as a new diagnostic class, separated from the personality disorders: the two disorders were then classified for the first time on separate axes, respectively I and II axis, with diagnostic specific criteria. A great distinction between substances abuse or addiction was made referring to disorder severity. In particular, the definition of addiction was referred to withdrawal phenomena[26]. The DSM-III criteria were, however, still unclear in some parts, giving

way to various diagnostic doubts, not allowing distinction between the two disorders (abuse/addiction). The DSM-III-R redefined the addiction concept, eliminating the distinction between physical and psychological addiction. Until then, the presence of tolerance or withdrawal was an essential criterion for drug addiction diagnosis. The concepts of "addiction" and "abuse" were also reviewed and better differentiated[27]. In 1994, DSM-IV reclassified these disorders, distinguishing substance abuse (abuse and addiction) from substance induced disorders (intoxication, delirium, etc.)[28,29]. Among the substances involved, there are also many drugs, such as anesthetics, analgesics, anticonvulsants, and various psychoactive substances. DSM-IV, unlike the previous DSM-III, erases the term "organic" and distinguishes three types of mental health disorder: induced by the substance use, due to a general medical condition and the disorders not related to any specific etiology. "Primary mental disorder" refers to those mental health disorders not induced by substance use and related to no general medical condition (in this case it is referred as "secondary mental disorder"). The DSM-IV-TR of 2000 also tracks the nosographic setting of the previous version. Within substance disorders, abuse is diagnosed when the repeated substance use leads to one or more social or professional problems; addiction is diagnosed when three or more criteria are involved, including different substance-related behaviors, as well as tolerance and withdrawal. While the definition of DSM-IV[30] and IV-TR[31] was a step forward in substance use insertion among psychiatric disorders, there were still some rigid categorical nosographic approaches at some points: differentiation between abuse and addiction in fact, appears too schematic, compared to the complex nature of the phenomena.

The ICD, in its 10th edition approved in Italy in 2000, classifies substance addiction within the diagnostic group of «psychic and behavioral disorders due to psychoactive substance use»[32]. In addition to the criteria used by DSM-IV, the craving for the substance, called "intense desire", is included. Diagnostic criteria are similar to DSM-IV ones, though less specific. Moreover, abuse is no longer considered an autonomous clinical entity with defined criteria, but as a disorder which in a specific way may cause «physical or psychological damage, including critical capacity impairment or inappropriate behavior, which may lead to disability or having adverse consequences in interpersonal relationships». As it can be seen, both DSM-IV (and IV-TR) and ICD-10 show strengths as well as critical issues in leading the clinician towards a clear understanding of the relationship between abuse and substance addiction and between substance use disorders and concomitant psychiatric disorders. From our point of view, the deepening and revised diagnostic criteria proposed in the recent DSM-5 version, published in 2013, and its "dimensional" approach may allow a better and more interesting reading of the phenomenon, orienting the clinician in the therapeutic issues[33].

DISCUSSION

Categorical and dimensional diagnosis: mutual synergy

The term "diagnosis" means both the process through which (δια-= through) you get to knowledge (γιγνώσκω=

knows) of the patient's psychic functioning, and the denomination, based on the clinical terminology, shared by the scientific community, which is attributed to this function. The result of the diagnostic process is a narrative systematic description, where it is possible, meeting the generalizability as well as specificity of the criteria. The diagnostic process can be both nomothetic, aimed to study the phenomena looking for the general elements that bound the individual patient to a defined group; both idiographic, aimed to study phenomena according to the individuality, looking for the elements that specifically characterize the disease and the individual patient's life story[34]. In addition, this process can follow categorical or dimensional systems. The categorical diagnosis is based on the mental health disease subdivision into diagnostic categories (i.e., schizophrenia, depressive disorder, anxiety disorder, etc.), referred to the presence or absence of specific symptoms, considered as diagnostic criteria. The categorical system is in line with the kraepelinian and neo-kraepelinian medicine and psychiatry tradition. The definition of "mental health disorder" that this approach underlines, conceives the state of illness as qualitatively different and separated from non-illness state, as well as each disorder would be clearly separated from the other. Dimensional diagnosis, on the other hand, classifies diseases as quantitative variations of dimensions/functions (relative to the severity of the disorder) distributed in a *continuum* ranging from psychopathological frameworks to "normality". The use of categories can be considered advantageous in many aspects, including: its remarkable simple use in the clinical setting, in the training and in the communication between operators; its eligibility in the epidemiological and psycho-pharmacological research; the ability to use diagnostic hierarchies. The categorical system followed by DSM, up to the Fourth Edition TR, in addition to the undoubted advantages, presents some limitations, such as the difficulty of insertion in the different categories "border clinical conditions", the need to use hybrid or residual categories for disorders not falling within the foreseen cases ("atypical", "not otherwise specified", etc.), the impossibility to clearly frame the "under-threshold" clinical situations and the high rate of patients with concomitant psychiatric disorders[34]. Hippocratic tradition, unlike Plato's school, at the dawn of medicine history, conceived a continuum between the state of health and disease[35]. Besides categorical nosographic settings, there are dimensional nosographic approaches, in which is postulated a *continuum* of gradations of the dimension investigated, which allows a better clarification[36].

"Psychopathological dimension" means «an altered psychic function, expressed by a set of indicative symptoms or signs, specific for the altered function»[37]. The dimensional setting reduces the risk of stigmatization associated with the use of diagnostic labels, facilitates and improves the "border cases" classification into the different categories, reduces the comorbidity[32] ("comorbidity" is the simultaneous presence of multiple diagnosis in the same patient: it is obvious that higher is the comorbidity, lower is the validity of the whole diagnostic system). In DD, it would be desirable to have a nosographic system which is clear, operational, and which allow the communication between different operators (categorical), but that is at the same time able to capture the numerous clinical relevant aspects and nuances critical for the patient's therapeutic project (dimensional). We believe that DSM-5 contribution may go in this direction.

Peculiarities and implications offered by DSM-5

As has been shown above, the current diagnostic pathway in the DD field is still affected by some nosographic faults, partially due to old legacies. On one hand, the distinction between primary and secondary psychiatric disorders is difficult, due to the complex and multifactorial nature of the phenomenon, making difficult the diagnosis with a paralyzing delay and poorer treatment efficacy! On the other hand, the use of rigid diagnostic categories makes hard to overcome the addiction/abuse dichotomy, and to grasp the behavior complexity and substance-related experience, not providing the clinician with those critical points essential to design an effective therapeutic intervention[38]. In the DSM-5, the new SUD diagnosis can be considered dimensional: the distinct diagnoses for abuse and addiction are combined into a single spectrum of eleven symptoms and based on the number of the symptoms, there is a greater or lower disorder severity[33]. In addition, the craving is present as a nosographic criterion: for the first time, the quality of the patient's life becomes a diagnostic criterion also thanks to the numerous studies in this field, starting with Anton's contributions in 1990s[39-41]. This new approach, as evidenced by the dimensional approach supporters, is more careful to subjectivity of each individual patient and able to provide a reliable and adhering clinical picture of the individual patient and of its various illness phases (detailing better the course), avoiding the categorical approach limits, in particular with regard to the problem of rigid and often "artificial" diagnostic borders and of generalized and not very careful individual patient's clinical pictures[42-45]. Furthermore, in DSM-5, more distinctly than in the past, we talk of substance-induced or substance-independent mental health disorders. AUD-induced disorders typically develop in close connection with alcohol intoxication/withdrawal and ameliorate with abstinence from the substance, even without specific treatment or therapy. The AUD-independent disorders, however, generally occur previously the AUD onset and require a specific therapeutic system. In this case we can properly talk of a DD.

Below are reported the DSM-5 criteria for substance-induced mental disorders[33]:

a. The disorder must have a significant clinical presentation of a considerable mental health disorder;
b. There is evidence from anamnesis, target examination or laboratory data for both the following conditions:
   1. the disorder developed during or within one month since the inoculation or abstinence or substance/drug intake;
   2. the substance or medicament involved is able to produce the mental disorder in question;
c. The disorder is not better specified by an independent mental health disorder. Such evidence may alternatively be:
   1. the disorder precedes the onset of severe intoxication or abstinence or exposure to the substance/drug;
   2. the disorder exhibits clinical relevance for more than one month since cessation of acute abstinence or severe intoxication or exposure to the substance/drug. (this criterion does not apply to possible persistent disorders, such as neurocognitive disorders);
d. The disorder does not occur exclusively during the delirium;
e. The disorder causes significant clinical distress, or significant difficulties in working-social function.

Basically, DSM-5 better details the dependent-independent concept, allowing to overcome the old and often "paralyzing" primary-secondary dichotomy asserting that, if:

1. psychopathological disorder exhibits clinical relevance (i.e., meets DSM-5 criteria) for a period longer than one month after complete abstinence (except for possible persistent disorders such as neurocognitive disorders);
2. there is a clinical history indicating an outbreak of psychopathological disorder prior to substance intoxication/abuse.

You are in front of a psychopathological disorder that is independent of substance use and as such it should be addressed readly and managed both from a pharmacological and psychotherapeutic point of view, based on the patient's general clinical picture.

Conflict of interests: the authors have no conflict of interests to declare.

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