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Books:

Kaplan HI, Sadock BJ. *Comprehensive textbook of Psychiatry.* Baltimore: Williams & Wilkins 1985.

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PSYCHOMOTOR AGITATION IN PSYCHIATRY: AN ITALIAN EXPERT CONSENSUS

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Key words: psychomotor agitation, assessment, management, de-escalation, pharmacologic treatment, restraint

Introduction

Psychomotor agitation (PMA) is a pathological condition characterized by a significant increase in ideational, emotional, motor, and/or behavioral activity that may be associated with a variety of psychiatric and medical illnesses. Currently, there is no unequivocal and unanimously acknowledged psychiatric definition for PMA [1]. The US Food and Drug Administration Center for Drug Evaluation and Research highlighted that the various definitions of agitation generally entail the presence of "exceeding restlessness associated with mental distress" and "excessive motor activity associated with a feeling of inner tension" [1]. Citrome [2] described the hallmark of PMA as excessive motor or verbal activity. Battaglia [3] designated agitation as a state of motor restlessness accompanied by mental tension, which in severe cases may lead to behavioral dyscontrol. The 2005 guidelines of the US Expert Consensus Panel for Behavioral Emergencies identified the following key features of clinically significant agitation that requires intervention in the emergency setting: abnormal and excessive verbal, physically aggressive, and/or purposeless motor behaviors; heightened arousal; and significantly impaired patient functioning [4]. However, aggression is not a core feature of PMA, and the frequency with which agitation and aggression are associated has not been clearly established [5 6]. The Project Beta (Best practices in Evaluation and Treatment of Agitation), fostered by the American Association for Emergency Psychiatry (AAEP), defined PMA as an extreme form of arousal that is associated with increased verbal and motor activity [7]. In the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), agitation is defined as "excessive motor activity associated with a feeling of inner tension. The activity is usually non-productive and repetitious and consists of behaviors such as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still" [8]. Irrespective of its definition, from a phenomenological point of view PMA is best considered as a transnosological syndrome [9], in which several pathological processes can converge.

An important feature of PMA, whatever its cause, is that its clinical manifestations go along a continuum ranging from a mere increase in ideation and behavioral activity to really acute and violent episodes [5 10].

If not adequately treated, PMA can rapidly escalate up to the highest levels of severity [11-13], with potentially dangerous behaviors and a high risk

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of personal injuries – for the patient, for accompanying people, for the staff – and property damage [3 5]. This progression is associated with increasing difficulties with the therapeutic approach, particularly with respect to preservation of patient dignity, humanity of care and therapeutic alliance with the physician. A further complication is that, in more severe levels of PMA, there is usually, although not necessarily, a decreased level of patient cooperation, with an increased risk of more invasive treatments and/or coercive measures [14].

As PMA is a symptom complex and not a nosological entity, currently there is no unequivocal therapeutic approach to this condition. Similarly, its evaluation, assessment and management often lack homogeneity and standardization, not only between countries but also within countries. In Italy, agitated patients may come to medical attention in rather different settings, for example, emergency departments (EDs), in-hospital diagnostic and therapeutic psychiatric services (DTPS), centers for mental health (CMH), assisted living residences, family medicine offices or their own homes, depending on the severity of agitation. The complexity of this scenario unavoidably implies that PMA episodes, at least in the initial stage, may be managed by different medical professionals (not only psychiatrists but also emergency physicians or other clinicians), thus favoring inhomogeneity of clinical approaches.

Causes of psychomotor agitation

Pathological states potentially associated with PMA [7] can be divided into the following main categories: internistic, surgical or neurological conditions, psychiatric disorders, and substance intoxications/withdrawals (Table I).

Internal medicine conditions include systemic infections, hyperthermia, hypovolemia, hypoxia, metabolic and electrolyte imbalances, endocrine disorders (especially thyrotoxicosis) and excessive doses of medications, particularly when they have psychotropic effects. The more common surgical causes of agitation are head traumas, severe burns, major surgery and the postsurgical period, especially in older people. In neurology settings, agitation episodes

Table I. Possible causes of psychomotor agitation.

Internal medical conditions	Systemic infections Hyperthermia Hypovolemia Hypoxia Metabolic imbalances (e.g., hypoglycemia) Electrolyte imbalances (e.g., hyponatremia, hypocalcemia) Endocrine disorders (e.g., thyrotoxicosis) Excessive doses of medications (e.g., psychoactive or antiseizure drugs)
Surgical conditions	Head traumas Severe burns Major surgery Postsurgical period in older patients
Neurological conditions	Central nervous system infections (e.g., encephalitis, meningitis) Epilepsy Postictal phase of seizures Brain tumors Intracranial hemorrhages Intracranial masses Metabolic encephalopathies (particularly from liver or renal failure) Cerebrovascular diseases Cognitive impairment*
Psychiatric conditions	Psychotic disorders Mania Agitated depression Anxiety disorders
Intoxications/withdrawals	Alcohol Recreational drugs (cocaine, ecstasy, ketamine, inhalants, methamphetamines, etc.) Environmental toxins

** In certain cases, cognitive impairment may be of both neurological and psychiatric interest.*

may occur in association with central nervous system infections, epilepsy, postictal phase of seizures, brain tumors, intracranial hemorrhages and other intracranial masses, metabolic and toxic encephalopathies, cerebrovascular diseases, and cognitive impairment/dementia. The main psychiatric causes of agitation include psychotic disorders, mania, agitated depression and anxiety disorders. Among substance intoxications/withdrawals, alcohol and recreational drugs play a primary role, but environmental toxins may also have importance.

This article focuses on PMA caused by psychiatric illnesses. However, it is worth noting that the potential causes of agitation reported in Table I are not an exhaustive list, and especially that these conditions may sometimes occur simultaneously in the same patient, thus playing a combined role or appearing as comorbidities. For example, it is well known that alcohol [15] and/or substance abuse [16 17] are particularly common in patients with psychotic or bipolar disorders, and that alcohol itself can cause a psychosis that is clinically different from both alcohol withdrawal syndrome and schizophrenia [18]. Consequently, PMA associated with intoxication or withdrawal states is strictly related to mental disorders, and is in fact encompassed in the psychiatric sphere of competence. Thus, in the presence of agitation, it is important not only to assess the behavioral and psychopathological features but also every other possible condition that could directly cause PMA or contribute to its onset. This means that for every agitated patient, when he/she is cooperative, the usual diagnostic path should always be completed, even when the clinical picture clearly suggests a psychiatric disorder.

The size of the problem

Despite the clinical impact of PMA and the fact that this syndrome is generally regarded as a widespread phenomenon in medical practice, data on its epidemiology as a separate entity are poor and inconsistent. Most of the available information comes from patient visits in the psychiatric emergency setting [19] and is therefore mostly related to agitation in psychiatric illnesses, with particular reference to aggression and violence. Even in these cases, however, data are not homogeneous and do not allow an accurate and systematic estimate of the incidence and prevalence of PMA.

In a recent Spanish study of over 355,000 hospital discharge records, 1.5% of patients had a diagnosis of agitation. Among people with PMA, 47.2% were women and 78% had two or more comorbidities, compared with 45.2% and 60.1%, respectively, in the control group. The mean age of patients with a diagnosis of PMA was 80.5 years compared with 68.3 years in the controls, thus suggesting that the main underlying condition was cognitive impairment. Among patients with agitation, hospital admissions related to an emergency situation were considerably more frequent than in the control group (91.5% *vs* 70.2%, respectively) [20].

In the general European population, the prevalence of psychotic and bipolar disorders has been estimated to be 1.2% and 0.9%, respectively; this corresponds to about 5 million and 3 million people, respectively [21]. Twenty-five percent of patients with schizophrenia and 15% of those with bipolar disorder have been shown to develop an average of two agitation episodes per year [22]. Furthermore, approximately 70% and 65% of these episodes, in schizophrenia and bipolar disorder respectively, have been classified as mild to moderate [22].

Prevalence rates of PMA ranging from 4.3% [23] to 10% [19 24-26] have been reported in psychiatric emergency services. In the United States, it was estimated that 21-28% of psychiatric-related emergency visits involved patients with psychosis, including schizophrenia [27 28], to which should be added 13% and 5% of visits for patients with bipolar disorder and dementia, respectively [28]. Considering that PMA is reported to be a “common symptom” in patients with schizophrenia, bipolar disorder or dementia who seek psychiatric emergency services [28-30], about 1.7 million visits per year in the United States are likely to involve patients potentially at risk for agitation [19]. Furthermore, in a multicenter Spanish study of 503 patients with schizophrenia admitted to hospital, agitation was the cause of admission in 60.4% of cases; 29.8% of patients had only agitation, whereas 30.6% were also aggressive [31]. In Italy, the Department of Mental Health at the University of Brescia conducted a study to assess how many patients admitted to hospital with a diagnosis of schizophrenia had PMA, at its different levels of dangerousness. Preliminary data showed that 62.6% of the 561 enrolled patients were agitated; all these patients had a Positive And Negative Syndrome Scale – Excited Component (PANSS-EC) score > 14, thus meeting the criterion for the need for specific clinical attention and immediate medical intervention [32].

In patients with bipolar disorder, agitation is often the main clinical manifestation during manic and mixed states [33-35]. PMA prevalence rates of 19.5% [36], 27% [37]

and 29% [38] were reported in cases of bipolar disorder I. Serretti et al. [39] reported a prevalence of PMA of 87.9% in bipolar disorder I and 52.4% in bipolar disorder II. According to Goodwin and Jamison [40 41], agitation is the third most frequent symptom in mania, with a prevalence of 87%. Interestingly, in a recent Japanese case series of 189 patients with major depressive disorder, agitated patients (39% of the total sample) had about a three-fold higher probability of mood switching to manic, hypomanic or mixed states, compared with patients without agitation [42]. Contrary to previous observations [43], these data suggest that PMA could be related to bipolarity in major depression [42].

Agitation is also very common in dementia. In more than 1800 frail elderly patients with dementia residing in 109 long-term care facilities, the prevalence of PMA was 10-90%, with a median of 44% [44]. In a 2005 study from India, almost all (96.7%) patients with dementia attending outpatient neurology clinics had agitation, with prevalence ranging from 93.2% in Alzheimer disease to 100% in frontotemporal dementia [45]. In Alzheimer disease, the frequency of PMA seems to increase in parallel with worsening of the patient's condition; for example, in a 2-year prospective study, prevalence increased from 33% to 50% during the observation period [46].

Of no lesser importance is the problem of aggression and violence in agitated patients. Although, as previously underlined, aggression is not an essential feature of PMA [6], agitation states can frequently result in violent behaviors [47]. In the United States, it was estimated that the average incidence of physical assaults on health care staff in EDs is 3.2 per nurse and 1.1 per physician per year, with schizophrenia and bipolar disorder accounting for 17.1% and 11.4% of incidences of aggression, respectively [48]. In a literature review of the incidence of aggression episodes in psychiatric adult patients evaluated by the Staff Observation Aggression Scale (SOAS), the number of such episodes in general psychiatric wards ranged from 0.4 to 33.2 per patient per year, with a mean of 9.3 per patient per year [49]. In the United Kingdom, between 1998 and 1999, there were 65,000 episodes of violence against National Health Service staff, and in mental health facilities, the average number of incidences of aggression was more than three-fold higher than the mean number observed in all UK health care facilities [50]. Yet in the United Kingdom, among patients experiencing a first psychotic episode attending psychiatric services, almost 40% had aggressive behaviors and about 20% were physically violent [51]. In a study of 253 patients admitted to a psychiatric ward, 21% had attacked persons during the 2 weeks before admission, and 13% during the first 24 hours of hospitalization [52]. Of over 5000 patients who were hospitalized for longer than 1 month, 7% had physically assaulted other persons in the hospital at least once within the previous 3 months [24]. In a retrospective Spanish study of 200 clinical records of patients admitted to hospital for acute psychosis between 1999 and 2001, 86% of patients showed signs of agitation and aggression during the hospital stay [53]. In another retrospective study that examined 102 violence episodes that occurred over the course of 5 months in the wards of a psychiatric hospital in London, 39% of patients with assaultive behavior had an affective disorder (mania) and 33% had schizophrenia [54]. In Italy, in a 7-year study of 3507 admissions to a psychiatric ward, the cumulative incidence of aggression was 11.6% per admission [55]. In another Italian study of 1324 patients admitted to public and private acute psychiatric inpatient facilities, 10% of patients showed hostile behavior (verbal aggression or violent acts against objects) during hospitalization and 3% physically assaulted other patients or staff members [56].

Aggression and violence are particularly frequent in schizophrenia. For example, in a retrospective German study that evaluated the clinical records of 2093 patients with schizophrenia admitted to the psychiatric hospital of the University of Munich between 1990 and 1995, 14% of patients fulfilled the ICD criterion for "aggression" at admission [57]. Among 289 patients with schizophrenia or schizoaffective disorder admitted to a psychiatric ward, 9% assaulted someone at least once during the first 8 days of hospital stay [58]. In a 2002 systematic review of epidemiology of violence in schizophrenia [59], the prevalence of violent episodes was 20% in the period preceding first hospitalization [60 61], 9% in the first 20 weeks after hospital discharge [62], and 8% in a large population study of over 10,000 adult patients [63]. Comorbidity with substance abuse increased the percentage of violence to 30% in the latter group. In patients admitted to hospital with a diagnosis of bipolar disorder, the prevalence of violent episodes in the first 20 weeks after discharge was 15% [59], whereas in elderly patients with dementia, aggressive behavior was reported in 57-67% of cases, with an annual incidence of 15.8% [64]. In Alzheimer disease, the proportion of physical assaults also ranged from 50% [65] to 64% [66].

Economic burden of psychomotor agitation from psychiatric causes

The costs originating from PMA due to psychiatric illnesses have not been evaluated systematically, because most studies have focused on the underlying diseases rather than on agitation per se. However, available data suggest that the economic burden of PMA, as well as the costs related to the inappropriate management of agitation and/or to potential coercive interventions, are significant. The factors that mainly influence the overall costs of PMA are the duration of hospital stay, the need for rehospitalization, and the cost of the hospital stay.

In the United States, Jaffe et al. [67] retrospectively reexamined data from 17 psychiatric hospitals, comparing 415 agitated and 1258 non-agitated patients; agitated patients had significantly lower probability of being discharged within 6 months and a significantly longer hospital stay compared to non-agitated patients (39% *vs* 69% and 164 *vs* 110 days, respectively). An Australian prospective study comparing 174 aggressive and 1096 non-aggressive patients, who were followed up for 18 months, showed that both the mean number of hospitalizations and the average duration of hospital stay were significantly higher in aggressive patients compared with non-aggressive patients (3.56 *vs* 1.75 hospitalizations and 24.9 *vs* 12.1 days, respectively) [68]. In another Australian prospective study, the length of hospital stay was 27.3 days for patients involved in serious aggressions, 23.3 days for patients involved in less serious aggressions, 14.4 days for patients not involved in serious aggressions, and 14.5 days in patients not involved in any aggressive episodes [69].

In Germany, Steinert et al. [70] retrospectively compared 96 patients with agitated or aggressive behavior and 42 patients without aggression or agitation admitted to a psychiatric hospital, and showed that the presence of aggression significantly increased the likelihood of rehospitalization. In a 3-year Norwegian prospective study of 98 patients involved in assault episodes and 836 non-aggressive patients, aggression was associated with a longer hospital stay and a significantly higher number of rehospitalizations compared with the absence of aggression (32.6 *vs* 9.7 days and 2.5 *vs* 1.5 rehospitalizations, respectively) [71]. Therefore, Rubio-Valera et al. [72], in the only currently available systematic review of evidence on costs and use of health resources due to PMA and restraint procedures in psychiatric patients, concluded that agitation has an important impact on these parameters, causing a prolongation of hospital stay and an increase of rehospitalizations and drug use. This in turn increases the economic and management burden of hospitalizations [73].

In the retrospective Spanish study [53] mentioned earlier, the average cost of hospital stay in the whole population of patients with acute psychosis was € 3228 (of which € 76 was for drugs and € 109 was for diagnostic tests), with a mean length of hospital stay of 21.8 days. When patients with (n = 175) and without (n = 25) agitation/aggression were compared, the cost of antipsychotic drugs was higher in agitated/aggressive patients (€ 71 *vs* € 17), whereas the length of hospital stay was similar (21.9 *vs* 21.1 days, respectively) [53]. In a recent pharmacoeconomic analysis by Cots et al. [20], the mean duration of hospital stay was 12 days among 5300 patients with a diagnosis of PMA, compared with 9 days among more than 350,000 control patients with similar characteristics but no agitation. In patients with PMA, the average costs increased by € 472 compared with controls; the increase reached € 1593 when a statistical model was applied in which all variables were assumed to be equal between agitated patients and controls, except for the diagnosis of agitation [20].

In another recent Spanish study, it was estimated that every episode of mechanical restraint among psychiatric patients has a total cost of € 513-1160, assuming a duration of 4-12 hours; on an annual basis, the estimate was € 27 million, based on a duration of 4 hours per episode [74]. In the United Kingdom, the estimated total direct cost for the management of conflicting behaviors in acute patients admitted to psychiatric wards for 2006 was £ 145,177 per ward, whereas the estimated cost related to restraint interventions was £ 212,316 per ward; on a national scale, these costs reached £ 72.6 million and £ 106.2 million, respectively [73]. The authors also calculated cost adjustments in the event of a 10% reduction in both the number of incidents and health staff costs, showing that in this case the annual national costs for conflict management and restraint interventions would have been reduced to £ 58.8 and £ 86 million, respectively [73].

Clinical manifestations

Independently of the psychiatric disorder underlying PMA, the clinical features are largely similar. However, if the same patient has several agitation episodes over time, these are not necessarily identical.

The first signs of PMA generally include motor rest-

lessness, decreased ability to maintain attention, hyperreactivity, irritability, inappropriate verbal and/or motor activity. At a more advanced stage, nervousness, anxiety, apprehension, stress, impulsivity, impaired self-control, verbal incontinence, accelerated speech, a tendency to altercation, aggressiveness, reduced cooperation, poor motor control, pacing, aimless wandering, sleeplessness, crying, confusion, weakness, headache, lack of appetite are variably present, often associated with autonomic signs, such as sweating, tachypnea, hyperventilation, tachycardia, dizziness. The clinical picture can evolve to anger, shouting, loss of control, explosive behavior, increasing anxiety up to panic, verbal and/or physical assault, loss of cooperation, violence, and self-harm. Symptoms of PMA proceed along a continuum of severity up to extreme levels of aggression and violence. Patients may go from a simple increase in verbal and/or motor activity (e.g., with repetitive sentences or movements, complaints, requests for attention, inappropriate dressing or disrobing gestures, inappropriate handling of objects etc.) to a more intense restlessness that can manifest both verbally (e.g., with screaming or curses) and physically (e.g., with continuous and aimless wandering, inappropriate entering or leaving places, more vigorous or threatening handling etc.), up to openly aggressive behaviors (such as verbal threatening, hitting, pushing, scratching, biting, throwing objects etc.) that may reach the highest level of dangerousness (e.g., intentionally hurting self or other persons, destroying property, suicidal or homicidal attempts). PMA is a "self-fueling" condition, in which patients draw upon their own apprehension to further increase their agitation, thus activating a vicious cycle that – if not halted – inexorably leads to the escalation of symptoms. Possible signs of this progression include continuous speaking, increased voice volume, increased speed and/or intensity of movements, invasion of personal space, muscle contraction, tension of facial and chewing muscles, etc. In the presence of these signs, immediate measures should be taken to stop the escalation before it reaches more dangerous levels.

Currently, there are no standard criteria for defining the severity of PMA. Traditionally and for clinical convenience reasons, three grades of agitation are usually recognized: mild, moderate and severe. However, this classification is largely based on clinicians' experience and judgement, rather than on the application of strict, unequivocal parameters. Some of the rating scales that have been developed over time (see below) provide cutoff values that allow a more objective evaluation, but these are not always easy to use in clinical practice, and the parameters on which they are based are not always homogeneous or systematically evaluable. Therefore, although a more extensive use of objective and consistent criteria is desirable, agitation is currently classified as mild, moderate or severe predominantly based on observation of patients and their behaviors, with the primary aim of making the right therapeutic choices.

Patient evaluation

In the evaluation of patients with PMA, particularly if they are unknown to the physician, the primary objective is to determine if agitation has an underlying medical cause. Therefore, if the clinical circumstances allow, an appropriate medical evaluation should be performed, together with attempts at verbal de-escalation, if possible. Once medical causes have been ruled out, a complete psychiatric evaluation must be done; this must be as thorough as possible and make use of adequate psychometric scales, when possible. However, as mentioned below, in daily clinical practice this "ideal" approach is not always feasible and may be challenging to pursue.

Medical evaluation in an "ideal" setting

A detailed description of medical evaluation in patients with PMA is beyond the scope of this article. However, even in the presence of individuals who are well known to the psychiatric services or with clear signs of a psychiatric illness, it is important to rule out underlying medical conditions that may trigger or exacerbate agitation [7].

When a person arrives with PMA, triage, initial assessment and de-escalation should occur at the same time [10], because they are all essential to correctly assess the patient and avoid delays in treatment. With the exception of cases in which immediate intervention is needed to prevent injuries to the patient or others, de-escalation should always be attempted together with any appropriate diagnostic examination, in an effort to reduce agitation and gain the patient's cooperation at the same time. However, both the diagnostic path and de-escalation should be halted if PMA reaches a level of severity that requires pharmacologic treatment and/or coercive measures to protect the patient, the staff and others from possible life-threatening events. Once this danger has been averted and the patient is less agitated, medical evaluation should be resumed, completing the history and physical examination.

It is important to obtain information – from the patient, accompanying persons and/or any available medical documentation – on potential comorbidities, traumas, substance abuse, intoxication, infections, metabolic or water and electrolyte imbalances, as well as on any other facts that could help make a correct diagnosis. Even during the evaluation of psychiatric patients, clinical history has a sensitivity of more than 90% for detecting medical problems, and physical examination has a sensitivity of more than 50% [75].

Anamnestic data or the presence of certain signs or symptoms can direct the diagnosis toward a specific underlying medical illness [7]. For example, PMA that appears for the first time after the age of 45 years is likely to be caused by a medical condition, as most psychiatric disorders have an earlier onset. Another reason to suspect a medical cause or comorbidity is the appearance of unusual symptoms in a patient with a known psychiatric disorder, whose previous symptoms were otherwise consistent over time.

If a patient experienced head trauma, this will often be reported in the clinical history or revealed by bleeding or contusions, headache, amnesia, altered consciousness, abnormal vital signs, confused speech or other motor problems [7 76]. Encephalitis or metabolic encephalopathies will probably cause mental confusion, inattentiveness and/or impaired judgement, or may be associated with physical symptoms such as motor incoordination, seizures or hemiparesis [7]; the simultaneous presence of fever, headache and neck stiffness, in particular, suggests encephalitis [77]. Generalized infections and sepsis may cause a high fever with possible seizures and disorientation [78]; hallucinations can also occur, especially visual ones, and are a common symptom in delirium, particularly in elderly patients [79 80]. Environmental toxins can cause a variety of symptoms, depending on the substance involved; the history will be very important in these cases, and the patient may show disorientation, somnolence and seizures beyond agitation [81]. Encephalopathy, cardiac arrhythmias, mental status changes, hemiparesis, seizures and abnormal neurologic findings can all be due to metabolic imbalances, such as untreated hypoglycemia and hyperglycemia, which are both easily reversible conditions [7]. In hypoxia, key signs include abnormal breathing patterns, dyspnea or tachypnea, and impaired oxygen saturation [7]. Untreated thyrotoxicosis may cause PMA, which will probably be associated with the typical clinical picture of heat intolerance, anxiety, palpitations, unintentional weight loss etc. [82].

If agitation is due to a postictal state, there should be a history of recent seizures and the patient may also be confused [83]. When a person ingests toxic levels of psychotropic drugs, disorientation, somnolence or agitation may be present [7]. Moreover, certain psychiatric medications can lead to life-threatening conditions such as neuroleptic malignant syndrome and serotonin syndrome. In both cases, tachycardia, hypotension and fever are usually observed, but in neuroleptic malignant syndrome the patient has “lead pipe” rigidity [84], whereas in serotonin syndrome myoclonus and hyperreflexia occur [85].

Alcohol and/or substance intoxication and withdrawal syndromes are common causes of PMA [86]. The clinical history may be revealing, but it may be difficult to obtain a reliable history from an agitated, intoxicated patient; abnormal vital signs, odor of alcohol, drug paraphernalia on the person, evidence of drug injection, or other similar clues are useful [7]. The patient may have disorientation, hallucinations, seizures, and autonomic instability [86].

If no medical cause is found for PMA, the patient can be seen by psychiatrists [7].

Psychiatric evaluation in an “ideal” setting

Psychiatric evaluation of the agitated patient starts with visual observation of his/her behaviors even before direct interview, paying attention to verbal and nonverbal interaction modalities during de-escalation [10]. During this phase, a team member can collect any useful information about the patient from family members, accompanying persons, paramedics, police officers, etc., and written medical material can be examined. These sources of data may be crucial in determining the cause of agitation, and often allow a medical cause to be suspected or ruled out.

Subsequently, it should be determined whether the patient has delirium [10]. In delirium, there is an altered level of awareness and signs of reduced attention, which should be searched for thoroughly because they can be subtle. Confusion, difficulties in concentration, perseverative behaviors, reactions to visual hallucinations, language impairment, problems naming or other cognitive deficits may be present, particularly in the setting of drug or medication use and medical illnesses. Moreover, the clinician should consider whether there is a chronic cognitive impairment that is contributing to PMA [10]. Although this deficit may be noticed directly by the examiner, information from family members or patient caregivers will be very useful, because the agitated patient with dementia is often not able to participate in a formal interview. The use of tools such as the Mini Metal State Examination [87] can be attempted to investigate the cognitive

status, but these instruments need patient participation and may have to wait until he/she is calmer.
The next point to consider is whether there is an intoxication or a withdrawal syndrome [10]. Knowledge of recent use of drugs or alcohol is important, and the *Diagnostic and Statistical Manual of Mental Disorders* can be useful in this task, because it includes specific diagnostic criteria for intoxication and withdrawal syndromes caused by common substances [8]. For example, alcohol withdrawal causes sweating, hand tremor, vomiting, transient hallucinations and anxiety, which are all easily observable by the examiner.
It should also be investigated whether agitation is related to psychosis; family members or other accompanying persons can provide information about this aspect [10]. If there is no psychosis but symptoms of mania are present, the treatment is the same as for the patient with psychosis [88]. In PMA due to nonpsychotic depression or an anxiety disorder, the underlying anxiety should be treated [89]; on the other hand, if the patient is simply angry or out of control, verbal de-escalation may work even in the presence of aggression [90].
When the patient is calm enough to undergo an interview, formal psychiatric assessment must be completed; there is no established standard evaluation, but the assessment should be as thorough as possible [10]. In particular, it should include a review of available clinical records and should cover the chief complaint, history of present illness, past psychiatric and medical history, substance use history, social and family history, as well as examination of mental status [10].
With regard to the chief complaint, it is worth considering both the patient perspective and that of other persons accompanying the patient, because they may be different; this can help to better understand the context in which agitation developed and what was the real issue that triggered the episode. History of present illness will provide valuable information to make the correct diagnosis. The time frame during which the symptoms developed should be explored, as well as stress factors identified by the patient and whether or not he/she has an adequate support system. Issues related to safety are also important, and the risk of suicide or violence should be openly discussed with the patient [10].
Past psychiatric history should explore previous contacts with psychiatric facilities, past diagnoses, treatment trials, hospitalizations, suicide attempts, history of violence, and current care providers. Medical history should include past medical illnesses and previous surgeries, paying special attention to head injuries including deceleration injuries [91].
Current medications taken by the patient are also an important issue, including over-the-counter drugs and alternative/herbal remedies. Allergies to medications should also be investigated [10].
Information should be obtained about alcohol or substance use, its impact on the patient's life, and any past treatment. These data should be supplemented with questions about smoking habits, caffeine intake, and other psychoactive substance use [10].
Social history can provide a better understanding of the patient's personality and should include developmental problems, level of education, problems with the police or justice system, work history, marriage status, affective and family relationships, child care, moral and spiritual issues. A history of physical or sexual abuse can provide clues to explain certain patient reactions (e.g., to restraint procedures), but examining these issues in depth is often not appropriate in the emergency setting. A family history should also be obtained, with particular attention to medical or mental illnesses and substance use, suicides, suicide attempts or self-inflicted injuries, because these events are risk factors for suicidal behavior in the patient [10].
The psychiatrist has to evaluate all components of the mental status, considering the patient's appearance and behavior, affective state and stability, thought processing, suicidal and homicidal ideation, the presence of psychotic symptoms, level of awareness and attention, concentration ability, judgement/insight, executive functioning, reasoning, and reliability [10]. The use of assessment tools such as the Mini Mental State Examination [87] or the Brief Mental Status Examination [92] can be helpful for cognitive evaluation, if they have not already been administered.
Addressing the risk of suicide or other violence is an important part of the psychiatric assessment of agitated patients, particularly in the emergency setting [10]. Although several scales have been developed specifically for this purpose, their usefulness in a busy and crowded emergency department is often limited. Furthermore, the power of these rating scales in predicting the imminent risk of suicide is generally poor. Consequently, a thorough examination of static and dynamic risk factors for suicidal or violent behavior is needed. Because relying solely on the patient's reports about his/her suicidal or homicidal impulses is not inadequate [93], judgement has to be based on a thorough mental state evaluation, on collateral information obtained from accompanying persons, and on the review of the patient's past behaviors. In assessing suicidality and homicidality, it is important to understand in detail the nature of violent thoughts,

including their frequency, duration, urgency, and how the patient copes with them, always keeping in mind that such thoughts exist on a continuum [10]. A particularly important issue is to check if the patient has access to guns, knives or blunt objects, because this is an easily modifiable risk factor with a great impact. Other significant aspects include previous suicide attempts or violence episodes, substance use, poor adherence to treatments, and limited patient support. At the same time, potential protective factors should be reviewed, such as profound spiritual beliefs, thinking that suicide and violence are immoral, feeling that children or other family members are under the patient's care, ability to identify reasons for living, and engagement in school or work. This process does not allow an exact prediction of suicide or violence, but it helps in forming a clinical judgement based on the available information, thus contributing to the estimation of the likelihood of these behaviors [10 94].

Assessment scales

In an attempt to standardize and make the evaluation of patients with agitation and/or aggression more objective, several scales have been developed over the past decades. Some are intended for general use, whereas others are destined for more specific populations (e.g., elderly patients, intensive care units, dementia, head traumas etc.) [5]. The scales that are most commonly used to evaluate PMA in multiple therapeutic contexts are listed in Table II, which also compares their main characteristics.

Some of these instruments were originally developed for use in limited settings, such as long-term care facilities (e.g., Aggressive Behavior Scale), acute post-traumatic phase of brain injuries (e.g., Agitated Behavior Scale), patient assessment by nurses or other caregivers (e.g., Brief Agitation Rating Scale), psychiatric wards (e.g., Brøset Violence Checklist), or elderly populations in assisted living homes (e.g., Cohen-Mansfield Agitation Inventory) [5]. However, they have also been shown to be effective in broader patient populations, in both research and clinical settings.

The Agitated Behavior Scale, which was initially conceived to assess agitation during recovery from brain injuries [95], has also been successfully used in psychiatric patients presenting in the ED [96]. It includes 14 items rated from 1 to 4 based on their level of severity, for a total score of 14 to 56. Cutoff scores for use in the setting of post-traumatic rehabilitation have been established that define four levels of agitation: absent (≤ 21), mild (22-28), moderate (29-35), and severe (≥ 36) [97].

The Cohen-Mansfield Agitation Inventory (CMAI) is a 29-item questionnaire that was mainly developed for the evaluation of elderly patients in long-term care facilities [98]. Each item is included in one of four categories ("factors") – physical/aggressive, physical/non-aggressive, verbal/aggressive, and verbal/non-aggressive – and is rated from 1 to 7 based on its frequency in the last 2 weeks; there are specific criteria for individual factors to define patient agitation. This instrument was also shown to be useful in the initial assessment of PMA in patients admitted to hospital for psychiatric care [5 99].

The Brief Agitation Rating Scale (BARS) was developed as a short form of the CMAI to allow a more rapid evaluation of agitation in patients living in nursing homes [100]. It includes 10 items that are rated from 0 (none) to 3 (often or continuous) based on their frequency in the last 4 days. Similarly to CMAI, BARS has been used in patients admitted to hospital psychiatric wards [5 101].

The Overt Agitation Severity Scale (OASS) has 12 items in three domains: vocalizations and oral/facial movements; upper torso and upper extremity movements; and lower extremity movements [102]. Items are organized within each domain based on their intensity, having an "intensity score" of 1, 2, 3 or 4; subsequently, they are rated from 0 (not present) to 4 (always present) based on their frequency during 15 minutes of observation. The severity score for each item is then calculated by multiplying the intensity score by the frequency. Initially created for elderly patients in psychiatric facilities, the OASS has also been validated in adult non-elderly patients [5 103].

The Positive And Negative Syndrome Scale-Excited Component (PANSS-EC) is a subscale of the PANSS (developed and standardized by Kay et al. [104] in 1987 for patients with schizophrenia), which takes into account only the excitation component [105]. It includes five items – excitement, poor impulse control, tension, hostility, and uncooperativeness – rated 1 (absent), 2 (minimal), 3 (mild), 4 (moderate), 5 (moderate-severe), 6 (severe), or 7 (extremely severe), for a total score between 5 and 35. A score ≥ 14 with a score ≥ 4 on at least one item usually indicates a clinically significant PMA [106-109], whereas a score ≥ 20 usually corresponds to severe agitation [110 111]. The PANSS-EC has been widely used as an assessment tool in clinical studies of pharmacotherapy for agitation [106-108 112 113]; response to treatment is generally considered as a ≥ 40% decrease in score within 2 hours [5]. However, this scale was validated only in recent years by comparison with other established psychometric tools,

Table II. Characteristics of the main scales used for the evaluation of agitation and/or aggression/violence.

Scale	No. of items/ domains	Rating	Criterion for rating	Total score	Cut-offs	Time needed to complete
Agitated Behavior Scale	14 items	From 1 to 4	Severity	From 14 to 56	14-21 = normal 22-28 = mild PMA 29-35 = moderate PMA 36-56 = severe PMA	30 minutes (physician) 8 hours (qualified nurse)
Cohen-Mansfield Agitation Inventory (CMAI)	29 items in 4 domains	From 1 to 7	Frequency during the last 2 weeks	From 29 to 203	Each domain has specific criteria	About 20 minutes (if information about the last 2 weeks is available)
Brief Agitation Rating Scale	10 items	From 0 to 3	Frequency during 4 days	From 0 to 30	No	4 days of observation
Overt Agitation Severity Scale (OASS)	16 items in 3 domains	Each item has a specific level of severity (from 1 to 4) within its domain and is rated from 0 to 4	Frequency during 15 minutes of observation	From 0 to 120	No	15 minutes
Positive And Negative Syndrome Scale-Excited Component (PANSS-EC)	5 items	From 1 to 7	Severity	From 5 to 35	Indicatively: 5-13 = absent/ minimal/borderline PMA 14-19 = mild to moderate PMA 20-35 = moderate/ severe to extremely severe PMA	A few minutes
Neurobehavioral Rating Scale-Revised (NRS-R)	29 items in 5 domains	From 0 to 3	Severity of interference with patient functioning	From 0 to 87	No	From 15-20 minutes to ~1 hour
Overt Aggression Scale (OAS)	16 items in 4 domains	Each item has a specific level of severity within its domain and is rated from 0 to 4	Severity	From 0 to 160	> 7 = violent patient	A few minutes
Aggressive Behavior Scale	4 items	From 0 to 3	Frequency during 7 days	From 0 to 12	No	7 days of observation
Clinical Global Impression Scale for Aggression (CGI-A)	1 item	From 1 to 5	Severity	From 1 to 5	Not necessary	Rapid
Brøset Violence Checklist (BVC)	6 items	0 (absent) or 1 (present)	Absence/ presence	From 0 to 6	0 = low risk 1-2 = moderate risk 3-6 = high risk	A few minutes

(continues)

(follows)

Table II. Characteristics of the main scales used for the evaluation of agitation and/or aggression/violence.

Scale	No. of items/ domains	Rating	Criterion for rating	Total score	Cut-offs	Time needed to complete
McNiel-Binder Violence Screening Checklist (VSC)	5 items	0 (absent) or 1 (present)	Absence/ presence	From 0 to 5	0-2 = low risk 3-5 = high risk	A few minutes
Historical, Clinical, and Risk Management-20 (HCR-20)	20 items in 3 domains	N (no = absent), P (possibly/ partially present), Y (yes = definitely present)	Absence/ presence during the last 1-6 months (Historical scale), during the current episode (Clinical scale) and as future risk for the 1-6 subsequent months (Risk scale)	Not applicable: answers are evaluated as a whole	The tool estimates as low, moderate or high the risk of: • future violence • severe physical injuries • imminent violence	From 20-30 minutes to a few hours

such as the Clinical Global Impression-Severity scale (CGI-S) and the Agitation and Calmness Evaluation Scale (ACES) [110]. In particular, a linear correlation was demonstrated to occur between PANSS-EC scores and those of the CGI-S, a 7-point, physician-rated, multifunctional scale that evaluates global patient severity. Agitated patients can be graded by CGI-S as 1 (normal), 2 (borderline agitated), 3 (mildly agitated), 4 (moderately agitated), 5 (markedly agitated), 6 (severely agitated), or 7 (the most extremely agitated) [114]. An average increase of 3.4 points on the PANSS-EC for each additional CGI-S point has been observed, according to the following scheme: 1 = 5-11; 2 = 12-14; 3 = 15-19; 4 = 20-23; 5 = 24-27; 6 = 28-32 [110]. Based on this correspondence, PMA can be indicatively classified by PANSS-EC as absent/minimal/borderline (5-13), mild to moderate (14-19), and moderate/severe to extremely severe (20-35).

The Neurobehavioral Rating Scale-Revised (NRS-R) is a multidimensional scale with 29 items divided into five categories: intentional behavior, emotional state, survival-oriented behavior/emotional state, arousal state, and language. Each item is rated from 0 (not present) to 3 (severe) based on how much it interferes with patient functioning [115]. The NRS-R showed good reliability in the evaluation of patients with recent closed head injuries [116].

The Overt Aggression Scale (OAS) includes 16 items in four domains: verbal aggression, physical aggression against objects, physical aggression against self, and physical aggression against other people [117]. Similarly to OASS, the items are organized within each domain based on their intensity, and are subsequently scored from 0 (not present) to 4 (always present) based on their frequency. This scale was designed for use in adults and children, in both research and clinical settings [5]. Several variants of the OAS have been developed over time, one of which – the Modified OAS (MOAS) – is a simplified version that rates only the most severe behavior within each domain [118]. As for OAS, MOAS scores range between 0 and 4, but the cumulative score obtained for each domain is multiplied by a factor specific to that domain: 1 for verbal aggression, and 2, 3, and 4 for physical aggression against objects, against self, and against other people, respectively. The MOAS has been used in psychopharmacological [119-121], genetic [122], and observational [70] studies, and an Italian version has been validated [123].

The Aggressive Behavior Scale is a 4-item instrument measuring verbal and physical abuse, socially inappropriate behavior, and resisting care [124]. Each item is scored from 0 (not exhibited) to 3 (occurred daily), based on its frequency during 7 days of observation. Originally developed for use in long-term care facilities, this scale has also been used for the evaluation of acute patients [5].

The Clinical Global Impression Scale for Aggres-

sion (CGI-A) is an easy-to-use tool based solely on observation of the patient; it was derived from the CGI-S with the aim of further simplifying its application in agitated patients, particularly with respect to the risk of assault [125]. In CGI-A, the original 7-point gradation of CGI-S is reduced to five points of aggressive behavior: 1 (absent), 2 (mild), 3 (moderate), 4 (severe), and 5 (overt). Similarly to CGI-S, CGI-A scores have shown to be linearly correlated with PANSS-EC scores. Each 1-point increase in CGI-A score corresponded to an average increase of 4.6 points in PANSS-EC score, according to the following scheme: 1 = 12.2; 2 = 16.7; 3 = 21.3; 4 = 25.8; 5 = 30.4 [125].

The Brøset Violence Checklist (BVC) was developed primarily to assess the risk of violence in psychiatric inpatients. It includes 6 items (confusion, irritability, boisterousness, physical threats, verbal threats, and attacks on objects), each rated as absent or present [126]. The total score is interpreted as follows: 0 = small risk of violence; 1-2 = moderate risk of violence (preventive measures should be taken); ≥ 3 = very high risk of violence (immediate preventive measures are required, and plans for handling an attack should be activated). In the study that validated the BVC, a score of ≥ 3 was predictive of a violent event in the next 24-hours [126].

The McNiel-Binder Violence Screening Checklist (VSC) is also intended to evaluate the risk of violent behaviors in hospitalized psychiatric patients [127]. It includes five variables – history of physical attacks or fear-inducing behavior within 2 weeks, absence of suicidal behavior, a diagnosis of schizophrenia or mania, male gender, and current marriage or living together with a partner – and each variable is rated as present or absent [5].

The Historical, Clinical, and Risk Management-20 Violence Risk Assessment Scheme (HCR-20) has been used to evaluate the risk of violence in several different settings. Initially developed in 1995 [128], it was recently updated to version 3 (HCR-20^{V3}) [129]. This instrument has 20 items in three domains: a historical scale (H, referring to “history of problems with...”), a clinical scale (C, referring to “recent problems with...”), and a risk-management scale (R, referring to “future problems with...”). Each item is scored as absent, possibly or partially present, and definitely present, to finally outline a global risk of violence that is “low or routine”, “moderate or elevated”, or “high or urgent” [129]. The HCR-20 has been found to be effective in clinical psychiatric, forensic, and correctional settings [5].

The actual applicability of these instruments in real-life clinical practice is highly variable, particularly if the patient has to be managed in emergency settings. For example, completing the HCR-20 may require several hours and needs information about past patient history, whereas BVC requires a few minutes to complete and is entirely based on currently observable behaviors [5 126].

It is important to remember that assessment scales provide a quantitative dimension of PMA intensity, but they should always be accompanied by a qualitative analysis of the problem and an etiological evaluation. In psychiatric patients who are already known to the mental health services, such an evaluation is likely to have been done during previous contacts. However, as repeatedly mentioned earlier, several concomitant medical, surgical, or neurological conditions may exacerbate, trigger or reveal agitation [7].

Moreover, it must be stressed that an assessment based on scales provides only a snapshot of the patient’s condition at a given time, whereas the severity of a PMA episode may change over time depending on the external environment and the evolution of the patient’s internal condition [5 130 131]. In practice, experienced psychiatrists and psychiatric nurses are able to accurately predict violent behaviors without the use of specific assessment tools [5], reaching an accuracy of more than 80% in newly admitted psychiatric patients [132]. Another limitation of the scales is that their use is often very difficult or impossible with the more severe patients, who require immediate interventions without leaving much room for formal evaluations.

Nevertheless, scales are useful tools for guiding treatment choices and should be used whenever possible, because they allow better standardization of therapeutic interventions and better planning of treatment procedures according to the severity of patient’s condition. From this perspective, PANSS-EC and CGI-S (or possibly CGI-A) seem to be particularly suitable for use in different clinical settings. They have the advantages of being easy to use, requiring only a few minutes to complete, being based only on patient observation without the need for his/her cooperation, providing cutoff scores that allow indicative differentiation between mild, moderate and severe PMA, having been validated in well-conducted studies, and being reliable and reciprocally correlated. Such characteristics make these instruments suitable for use in the emergency setting, as well as in any situation in which it is not possible to administer more complex scales due to time or environment problems.

Patient evaluation in real-life psychiatric practice

As mentioned previously, it is not always possible to carry out a complete and thorough evaluation of the agitated patient in daily clinical practice. Indeed, the diagnostic approach often has to be adapted to the very different, sometimes challenging conditions in which the psychiatrist usually works. In particular, experience in the field shows that there are usually three factors that can affect the way patients are assessed: whether the patient is already known to psychiatric services or not; the setting in which the evaluation is done (patient's home, ED, CMH, DTPS, and in-hospital consultations are among the most common); and the severity of agitation (mild, moderate, or severe).

In known patients, the assessment will be focused essentially on ruling out new medical conditions that can alter an otherwise acknowledged clinical situation, and on investigating the relationships between such conditions and the current episode of agitation. If medical illnesses are not identified, the patient can be referred for psychiatric treatment.

In patients who are not known to the physician, medical and psychiatric evaluation is necessary to provide treatment as appropriately as possible. With regard to the setting, the likelihood of facing unknown patients is highest in the patient's home and the ED. In CMH and DTPS, patients are usually well known to the psychiatric service, either because they have been followed for a period by the community facility (i.e., the CMH) or because they were previously admitted to the psychiatric hospital (i.e., the DTPS). Even when a patient is newly admitted to DTPS, he/she usually comes from the ED, where his/her clinical history was investigated and a psychiatric problem was identified that warranted referral to a specialized ward. Similar considerations apply for in-hospital psychiatric consultations requested by non-psychiatric wards; in this case, all the medical and/or surgical evaluations will have been done by the attending physicians, and the psychiatrist should only examine mental health problems.

In unknown patients who are visited at home, medical evaluation can be carried out only if PMA is mild, and will be necessarily limited to basic parameters such as blood pressure, heart rate, breathing or body temperature. For any other detailed assessments, and in the case of a more serious agitation (i.e., moderate/severe) in which the patient is likely to be less cooperative, referral to hospital (primarily the ED) will be necessary. In this way, a diagnostic and therapeutic plan can be initiated that will not only be more appropriate but also more protected and safer.

With regard to the evaluation of unknown patients in the ED, here physicians have all the equipment and diagnostic procedures needed to identify potential medical causes for PMA. Therefore, the only factor that will influence a thorough clinical examination – medical at first and psychiatric thereafter – is the level of the patient's agitation. If PMA is moderate or severe, a more rapid assessment is warranted so that preference can be given to the treatment to prevent symptom escalation. However, lack of information in the ED setting may be often overcome by a direct access into the computerized network of the community psychiatric services, which are connected to the hospital. This may facilitate the evaluation of patients who are otherwise unknown to the emergency physicians.

Therapeutic approach

Regardless of the causes, PMA is a condition that requires an early and sometimes immediate intervention to control symptoms, reduce the risk of injury [5], and prevent escalation and its potentially very dangerous consequences. At the same time, it is essential to adopt a comprehensive approach that respects the dignity of patients, involving them as much as possible in therapeutic decisions. In particular the preferences of the patient should be accepted as much as possible and the "therapeutic alliance" should be preserved. From this perspective, invasive treatments should be avoided as much as possible and coercive measures should be used as little as possible, limiting their application to cases in which they are absolutely necessary and only for the time that is strictly needed. All of this helps to avoid the stigma that often accompanies psychiatric patients, particularly when they present in a state of agitation. Such an approach is in line with the contents of a recent document from the Italian National Committee for Bioethics on the ethical problems of restraint [133], as well as with the true spirit of Italian Law No. 180 of May 13, 1978 [134], according to which compulsory mental health treatment represents a clear failure of the strategies of protection and implementation of mental health.

When patients with PMA are under observation in emergency conditions, the aims of their psychiatric management should be the following: rule out that the symptoms have a medical cause; quickly stabilize the acute crisis; avoid the use of coercive meas-

ures; deliver treatment in a setting as unrestrictive as possible; establish a therapeutic alliance; ensure that the patient's care is undertaken and plan a post-treatment path [135].

De-escalation

The first approach to an agitated patient should always begin with verbal de-escalation, accompanied by appropriate environmental changes and any other strategies that can positively engage the patient [135]. De-escalation should be used systematically in all cases of PMA, with the objective of preventing worsening of symptoms and thus avoiding the need for physical restraint [135].

The latest version of Project Beta [90] and the 2015 NICE guidelines on the management of violence and aggression [136] may also be applied to the broader case of PMA, because they describe how to carry out de-escalation correctly, including through the creation of a structurally adequate environment. Firstly, a suitable setting is necessary, especially with regard to safety (easily removable furnishings, absence of blunt objects, reduction of bothersome sensory stimulations, adequate exits etc.). Secondly, it is essential that the health staff involved have a high level of expertise and professional skills and have been properly trained in this area. Moreover, there must be an appropriate number of operators (ideally 4-6) to ensure safety if an episode of PMA results in violence. Finally, the use of assessment scales should be encouraged, because they may help to avoid staff members underestimating or ignoring the early signs of escalation [90].

Once these environmental and professional conditions are in place, the correct execution of de-escalation requires the adoption of a series of attitudes and behaviors that can be summarized as follows [90 136]: respect the patient's personal space and protect one's own security, reassure the patient and ensure a certain margin of safety; avoid attitudes (including nonverbal ones) that may be perceived as provocative by the patient, and thus may be at risk for triggering symptom escalation; establish verbal contact, designating a single person who will speak with the patient and be responsible for conducting de-escalation; be simple, concise and reassuring in speaking, and repeat concepts if necessary; identify patient's wants, understand his/her desires and feelings, show empathy and express the will to help; listen carefully to what the patient is saying by the use of so-called "active listening", which better helps the patient to define sensations he/she might find difficult to express; express agreement with the patient, also using generic or indirect statements if necessary, and start from this agreement to express disagreement; set clear limits between acceptable and unacceptable behaviors, while being respectful yet firm; offer choices and alternatives, particularly with regard to violence, and infuse optimism and serenity, by having attitudes that facilitate relaxation; if coercive measures are needed, re-examine the event with both the patient (so that he/she can better understand the need for intervention and the inner reasons that led him/her to precipitate the situation) and the staff involved (so that suggestions can be exchanged to improve management of future episodes). Such an approach can potentially reduce the level of agitation and the risk of associated violent episodes. Current clinical thinking tends to limit coercive measures as much as possible, making the agitated patient a collaborative partner who is constructively engaged in the management of his/her own behavior. This will not only help in calming the patient without using forced treatments, but also and above all will preserve the patient's trust in health professionals, thus increasing the likelihood that he/she will seek their help again in the event of future episodes [90].

Pharmacological therapy

When de-escalation fails to achieve the desired results, or when there are no margins for adopting verbal strategies, it may be necessary to use medications. The main goal of pharmacological therapy in PMA is to rapidly calm the patient without excessive sedation [4 135 137 138]. This allows interaction and collaboration with the patient to be preserved, and the diagnostic and therapeutic path to be continued in a constructive manner [5 138].

Medications

It has been postulated that the fundamental characteristics of an "ideal medication" for the acute management of PMA include the following: easy preparation; nontraumatic administration (in particular, without the use of needles); no associated pain or need for physical restraint; rapid onset of action; little interpatient variability in pharmacokinetics and pharmacodynamics; a sufficient duration of effect for patients to be transported to the appropriate service; calming the patient without excessive sedation (thus allowing interaction with the patient, diagnosis, and/or selection of additional therapies); a low risk for adverse reactions and drug interactions; and the ability to control PMA also in patients with underlying conditions that may not yet be fully understood [5 139 140]. At present there is no gold standard medication for the treat-

ment of all cases of PMA, but three classes of drugs are used most frequently for this condition: first-generation (or typical) antipsychotics (FGAs), second-generation (or atypical) antipsychotics (SGAs), and benzodiazepines [1 135 138].

First-generation (typical) antipsychotics. FGAs have been used for a long time in the treatment of PMA. Although the exact mechanism of their calming effect is not completely understood, it is most likely due to inhibition of dopamine transmission in the brain, which in turn reduces the psychotic symptoms causing agitation [138]. However, the antipsychotic effect is not fully comparable with the anti-agitation effect, because control of psychotic symptoms generally requires a wider timescale.
Among the FGAs, phenothiazines tend to cause more hypotension, more anticholinergic side effects, and a greater reduction in the seizure threshold, compared with butyrophenones. Therefore, these are not the drugs of choice for the treatment of acute agitation [11 138]. The butyrophenones haloperidol and droperidol do not significantly interfere with vital signs and have negligible anticholinergic activity and minimal interactions with other non-psychiatric medications [138]. Haloperidol, in particular, is the most common FGA currently used to treat acute agitation. However, both these compounds are associated with major, potentially dangerous side effects, first and foremost QTc interval prolongation and extrapyramidal effects, such as dystonia and neuroleptic malignant syndrome. Although the extent and actual clinical significance of QTc prolongation induced by haloperidol and droperidol is still debated, cases of torsades de pointes have been reported with both drugs [138]. Therefore, they should be used with caution, especially in patients with heart disease, in those who are taking other medications that can prolong QTc, and in patients with conditions predisposing to QTc prolongation or torsades de pointes, such as electrolytic imbalances or hypothyroidism. Moreover, in all these cases, it seems prudent to avoid intravenous administration of haloperidol [138]. The frequency of extrapyramidal side effects is not clear, but incidence rates of up to 20% have been reported in agitated patients treated with haloperidol alone, compared with 6% in those treated with a combination of haloperidol and lorazepam [141]. Other studies have shown a similar reduction in extrapyramidal effects when haloperidol was combined with promethazine [142]. Therefore, haloperidol is now frequently administered in combination with one of these drugs. However, because most SGAs (atypical) are equally effective in the treatment of PMA, have low rates of extrapyramidal side effects and are frequently subjectively preferred by patients over FGA [143 144], current guidelines consider FGAs to be less preferred than atypical antipsychotics [138]. Nevertheless, it has been proposed that haloperidol may remain the medication of choice for PMA due to acute alcohol intoxication, because SGAs have not yet been studied enough in this situation [138].
FGAs also include loxapine, which shares several characteristics with atypical antipsychotics, including the antagonist effect on 5-HT2A receptors [145]. An inhaled formulation of loxapine has been developed and recently approved [146 147], and has been shown to be effective in the treatment of acute PMA [109 148 149].

Second-generation (atypical) antipsychotics. Similarly to FGAs, SGAs act as antagonists at the dopamine D2 receptors but have a comparable or stronger antagonistic effect on other receptor types, particularly 5-HT2A. In addition, they have actions at other receptor types (such as histamine, norepinephrine, and α-2 receptors) with varying degrees of potency depending on the individual drug [138]. Compared with FGAs, atypical antipsychotics are associated with a much lower risk of side effects such as dystonia or akathisia, with incidence rates of less than 1% [150-152].
The list of the most commonly used SGAs in the acute setting includes olanzapine, asenapine, ziprasidone, aripiprazole, risperidone, paliperidone, and quetiapine. All these drugs have been shown to be more effective than placebo and at least as effective as haloperidol in the treatment of PMA, both in oral and parenteral formulations [138]. Although there are no head-to-head studies of SGAs in the acute management of agitation, attempts have been made to compare the effectiveness of different drugs on a common basis using indirect parameters [153]. These studies have generally indicated that most atypical antipsychotics are equally effective in reducing symptoms, with three possible exceptions: (a) aripiprazole is slightly less effective than the other SGAs; (b) quetiapine, despite its benefits in hospitalized patients, is associated with a high risk of orthostatic hypotension in the ED, where patients are often volume depleted; (c) clozapine is a last-chance option that must be reserved for treatment-resistant patients with schizophrenia [138].
Most of the SGAs have not been studied in patients with alcohol intoxication or in combination with benzodiazepines. Therefore, alcohol intoxication is better treated with a typical antipsychotic, especially if the physician intends using a benzodiazepine as well [138].

Benzodiazepines. Benzodiazepines, such as diazepam, lorazepam and clonazepam, act on the GABA receptor, the main inhibitory neurotransmitter in the brain [138]. These medications have well-known efficacy in the treatment of PMA, and are often preferred to other compounds when agitation is due to alcohol withdrawal or stimulant intoxication, as well as when the cause is undetermined [138]. In contrast, in agitated psychotic patients, benzodiazepines alone may only sedate the patient without addressing the underlying condition causing PMA. Moreover, benzodiazepines may induce excessive sedation, and have the potential for respiratory depression or hypotension when administered parenterally in patients with respiratory diseases, or in combination with alcohol or other central nervous system depressants [138]. In the rare situation when a patient develops psychotic symptoms as a result of chronic abuse of stimulants (particularly amphetamines), an FGA or an SGA can be added to benzodiazepines, or can be used instead of them [138 154].

Routes of administration

In addition to traditional oral or parenteral medications, the therapeutic armamentarium for PMA has expanded in recent years with new formulations such as orodispersible tablets, sublingual preparations, transdermal patches, and inhaled formulations. Similarly to the selection of the drug to be used, there is no ideal route of administration that exactly meets the therapeutic needs of all patients with agitation; rather, each route has advantages and disadvantages that should be well understood to make an appropriate choice for the individual patient.

Oral route. Oral formulations, which are widely available for all three categories of medications examined above, are generally preferred to parenteral preparations for the initial treatment of PMA [138] due to their non-invasiveness, ease of use, acceptance by patients and efficacy. Their main limitation is the slow onset of action [146 155], which needs 20-30 minutes to 1-6 hours for maximum therapeutic effect. For this reason, oral formulations are not the best choice when rapid action is required to control intense or quickly worsening symptoms. Another possible problem with oral drugs is that agitated patients can "cheek" tablets (taking, but not swallowing), thus nullifying the effectiveness of their absorption process [135 140]. Oral formulations are therefore associated with a higher risk of poor treatment adherence, and so require thorough patient monitoring by the medical staff. Some of these limitations can be partially overcome with sublingual formulations [155 156] or rapidly orodispersible tablets, but their use in PMA has not yet been studied extensively.

Intramuscular route. Intramuscular (IM) formulations, which are also widely available for all medications commonly used for PMA, have the advantage of a more rapid onset of action compared with oral preparations, generally achieving their maximum effect within 15-60 minutes [138]. However, their use carries a higher risk of adverse events and, for obvious reasons, patient reluctance [135 155]. Except in the rare cases when the patient asks for their use (e.g., because he/she has already experienced the efficacy of a given IM medication and/or fears of rapid escalation of symptoms), IM medications are generally perceived as an invasive and coercive therapeutic option that violates the patient's personal sphere. Therefore, from the perspective of respecting the patient's dignity and preserving "therapeutic alliance", an effort should be made to limit the use of IM formulations as much as possible, with a preference for less invasive options [135 138].

Intravenous route. Intravenous (IV) medications have the advantage of providing an immediate onset of action, because the drug enters the bloodstream directly and exerts its maximum effect within a few minutes [138]. However, IV formulations magnify the inherent limitations typical of IM drugs. In particular, IV medications are generally less easy to use, less manageable and, if patient is non-consenting, require more efficient immobilization than IM preparations. IV medications are usually perceived as an even more invasive therapeutic option compared with IM formulations, and therefore, for the same reasons as discussed above, other modes of administration are now recommended [135 138]. Furthermore, as mentioned previously, their use is clearly contraindicated in some situations, e.g., IV haloperidol in patients at risk of QTc prolongation or torsades de pointes.

Transdermal route. A nicotine-containing transdermal patch has been used with good results in patients with schizophrenia who smoke and have PMA, showing its superiority compared with placebo [157].

Inhalation route. The latest innovations in the treatment of PMA are inhaled medications, which can ensure an ultra-rapid onset of action, even faster than IM formulations [145]. Inhaled loxapine, which is administered through a dedicated device, is absorbed via the lungs, and passes very quickly into the systemic

circulation, and thus has pharmacokinetic parameters similar to those of an IV preparation [146 147]. Several studies have demonstrated its efficacy versus placebo in the treatment of agitation [109 148 149], and other studies are currently underway to compare this formulation with midazolam and aripiprazole [135]. In addition to being effective and very fast (a characteristic that is always desirable in agitated patients), inhaled loxapine is non-invasive, it calms patients without sedating them, it couples an antipsychotic effect with the control of agitation symptoms, it is administered at a much lower dose than oral loxapine, and it has no clinically significant side effects. Many of these properties correspond to those of an "ideal medication" for the treatment of agitation [5 139 140] and make inhaled loxapine a valid non-invasive therapeutic option to be preferred over parenteral formulations just like oral drugs [135].

General principles for the use of medications

The guidelines developed in 2012 as part of Project Beta [138] provide some useful general recommendations for the use of medications in the treatment of PMA. These recommendations have been confirmed and expanded by a recent international consensus document on the assessment and management of agitation in psychiatry [135]. Firstly, the use of medications as a restraint (i.e., to restrict movements) should be avoided; in contrast, a provisional diagnosis of the most likely cause of agitation should be attempted, so that the most likely disease can be targeted by therapy. Secondly, non-pharmacological strategies, such as verbal de-escalation and reducing environmental stimulation, should be attempted before medications are administered. As discussed earlier, pharmacologic therapy should be used to calm patients rather than sedate them by inducing sleep. Moreover, patients should be involved as much as possible in the process of selecting medication, taking into account their preferences and explaining to them the benefits and potential disadvantages of the various options in a simple, calm and comprehensible manner. This is particularly true for the selection of the route of administration, which can be strongly associated with possible negative feelings of invasion and violation of the patient's personal sphere; in this sense, inhaled formulations are now added to oral drugs as a non-invasive option that is readily accepted by patients. In general, non-invasive treatments are preferred over invasive treatments whenever possible. In addition, IV treatment should always be avoided, except in cases where there is no viable alternative [135 138].

In mild PMA, oral medications – including sublingual and liquid formulations and orodispersible tablets – are preferred over parenteral ones. In mild or moderate PMA and in all cases in which a rapid onset of action is required, inhaled formulations can be considered. In other words, when the patient maintains a good level of cooperation, the oral and inhalation routes of administration are preferred over the parenteral route. In severe PMA, speed of action and reliability of drug release are the most important variables that must be taken into consideration in selecting the route of administration [135].

In the event of agitation due to alcohol withdrawal, benzodiazepines are preferred over antipsychotics; in contrast, if agitation is due to alcohol intoxication, antipsychotics are preferred over benzodiazepines. For PMA caused by intoxication with stimulants, benzodiazepines are generally considered first-line agents, except in the case described earlier of psychotic symptoms from chronic amphetamine use, for which SGAs may be useful in addition to benzodiazepines. For agitation caused by severe mental illness – such as schizophrenia and bipolar disorder – there is an indication for preferential use of antipsychotics. In this case, SGAs are preferred over FGAs. If the initial dose of an antipsychotic medication is insufficient to control PMA, adding a benzodiazepine is better than increasing the dose of the same antipsychotic or adding a second antipsychotic. For agitation associated with delirium (except when a medical illness, alcohol intoxication or withdrawal, benzodiazepine withdrawal, or sleep deprivation are present), if immediate control of symptoms is needed, SGAs are the preferred agents. Low-dose haloperidol is an acceptable option, whereas benzodiazepines should be avoided because they can exacerbate the delirium [135 138].

Restraint and seclusion

The term "restraint" indicates any method aimed at immobilizing the patient or reducing his/her ability to freely move arms, legs, trunk or head [158 159]. In this context, it is important to distinguish between mechanical and physical restraint. The first procedure is ancient (Fig. 1) and implies the use of dedicated devices or equipment, whereas the second is a practice done manually by operators and is generally limited to the time required to administer therapies. When mechanical restraint is carried out, physical restraint necessarily precedes it. The term "seclusion" refers to the involuntary solitary confinement of a patient alone in a space from which he/she is physically prevented from leaving [158 159].

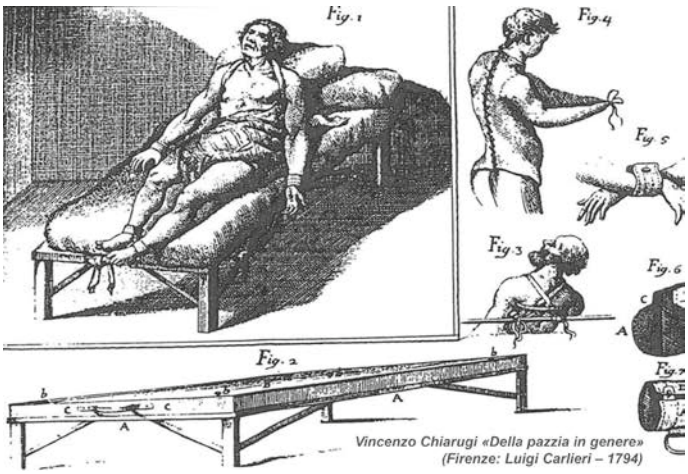

FIGURE 1.
The most commonly used methods for mechanical restraint in the eighteenth century. (From Chiarugi's treatise "Della pazzia in genere", published in 1794 by L. Carlieri, Florence, Italy).

The clinical situations concerning restraint and seclusion vary greatly from one country to another, mainly depending on local legislation and on whether appropriate facilities and equipment are available. In Italy, seclusion is almost never practiced, particularly in the ED, partly because there are no suitable spaces for it to be accomplished appropriately. A detailed description of the correct methods for implementing coercive measures is beyond the scope of this article; for an exhaustive discussion, please refer to the 2015 NICE guidelines [136]. For our purposes, it is appropriate to point out some general aspects.

Restraint and seclusion are coercive measures that should be avoided whenever possible, but they are life-saving interventions in particularly serious conditions. Therefore, they should be used only as a last resort in cases of extreme necessity, when other non-coercive strategies have proven to be ineffective, and when they are the only available means to prevent imminent injuries. If there is a risk of violence, it is necessary to protect the safety of the patient, the health care staff and any other people present [135]. These measures are potentially harmful to the patient's dignity and can compromise the doctor-patient relationship and therapeutic alliance, in addition to being associated with the risk of injury and harm. However, sometimes they are necessary to resolve PMA episodes that cannot be addressed by other methods. In Italy, restraint and seclusion are regulated and monitored by specific institutional and regional procedures.

In the case of restraint, it is essential to actively monitor the patient, regularly documenting his/her condition. In the first hour, vital signs should be recorded every 15 minutes, whereas in the next 4 hours they can be checked every 30 minutes. The patient should be assessed or reassessed as soon as possible by qualified personnel, and a patient should never be left for a long time without being assessed. Both restraint and seclusion should be discontinued as soon as possible, when the patient is no longer considered to be dangerous to himself/herself and/or others [135].

Moreover, it should be borne in mind that the effectiveness of seclusion and restraint is not sufficiently supported by empirical evidence [50 160], and that they can have serious physical and psychological consequences for all the people involved [159]. In addition, if the patient perceives a high level of coercion, this reduces his/her satisfaction with the treatment [161] and may decrease the likelihood that he/she will return to the psychiatric service to continue follow-up and therapy [162] Whatever happens during a crisis is bound to influence the way a patient will perceive the next treatments [163]. If the patient feels that therapeutic intervention has been forced upon him and led to a further loss of control, he/she will tend to associate treatment with loss of control in the future. In other words, every time an intervention is performed as part of the treatment for a crisis, clinicians should consider carefully the patient's first impressions, because these may affect – among other aspects – future adherence to therapy, an thus have long-term consequences [163]. In addition, reduction or elimination of coercive procedures may be associated with economic savings and an improved cost-benefit ratio, because it reduces injuries to the patient and health care staff, claims for damages by employees (with their associated costs), liabilities, time expenditure by the staff (with its associated costs), staff turnover and episodes of absenteeism [72].

All these considerations confirm that coercive measures, as already discussed, clearly contrast with the principles recently expressed by the Italian National Committee for Bioethics [133] and with the spirit of Italian Law No. 180 [134].

Therapeutic approach in real-life psychiatric practice

Similarly to what happens for patient evaluation, in real-life clinical practice treatment is also strongly influenced by the three factors considered above: knowledge of the patient by psychiatric services, the setting in which patient is managed and the severity of PMA.

Treatment of an already known patient is simplified and is mainly focused on the disease responsible for

the state of agitation. In this case, therapy (whether pharmacological or not) will mainly depend on the clinical setting and the severity of agitation. At home and in CMH, patients can be managed only in the initial and milder stages of PMA, during which, while verbal de-escalation is certainly feasible, pharmacological treatment is only limited to drugs available in non-invasive formulations (i.e., either oral or inhaled). Obviously, in these cases the same considerations apply that were outlined in the previous sections and that are expressed in guidelines and consensus documents: if alcohol withdrawal is suspected, benzodiazepines are preferred over antipsychotics; if alcohol intoxication is suspected, antipsychotics are preferred over benzodiazepines; and when a psychiatric illness is present, antipsychotics are indicated, with a preference for SGAs over FGAs [135 138]. At the patient's home and in community facilities such as CMH, the management of severe PMA – in which patients mostly lack a sufficient level of cooperation to carry out treatment in a responsible and collaborative manner – requires referral to hospital for more appropriate assessment and monitoring.

In hospital, either in the ED or in DTPS, already known patients can be managed in an appropriate manner based primarily on the severity of agitation, ranging from non-invasive treatments (oral and inhaled) for mild and moderate forms, to invasive treatments and possibly restraint measures – if they are the only feasible option – for more severe episodes. In these contexts, the selection of pharmacological treatment should obviously be in line with recent recommendations, whenever possible favoring rapid-acting, non-invasive, well-tolerated formulations that can calm the patient without excessive sedation [135 138].

The treatment of patients who are unknown to the clinical staff taking over their care is certainly more complex, and is necessarily subject to a preliminary assessment. Patients with mild/moderate agitation for whom preliminary assessment is done at home or in CMH can be managed with verbal de-escalation and/or non-invasive pharmacological therapies in the same settings. Other cases – i.e., patients with moderate/severe PMA and those with mild PMA who go directly to hospital – will be managed in the hospital setting, which facilitates their assessment, treatment and monitoring. In both the ED and DTPS, the therapeutic strategy will be selected based on the severity of agitation and on the level of cooperation from the patient. When the degree of PMA allows, less invasive formulations are also preferred over more invasive strategies in these settings. However, while the oral route is restricted to patients with mild PMA in whom rapidity of action is not an absolute priority, the inhaled formulation is not only non-invasive but also achieves its maximum effect as rapidly as IV drugs; therefore, inhaled medication can be considered as a valuable therapeutic option in patients with moderate PMA, in whom the speed of calming action is critical to prevent escalation. However, in cases of severe PMA when the patient is not cooperative, IM formulations (preferably without restraint) are still the only way to stop symptom escalation and prevent harm to people and/or property.

Unmet clinical needs and future perspectives

In light of the concepts discussed here regarding the management of such complex patients, the importance of an early approach to PMA, particularly in community settings such as CMH and residential facilities, must be stressed. This allows more effective prevention of escalation, and it is easier to preserve the ethics of treatment at this phase of agitation by adopting non-invasive therapeutic strategies. From the perspective of future research, there is also a need to identify reliable clinical predictors of PMA that could help physicians to recognize patients at higher risk of agitation and manage them properly. Furthermore, a multidisciplinary clinical approach to these patients should be favored, especially in the hospital setting – where cooperation between different professionals is easier, also in organizational terms – and in patients who are not already known to the services. In this way, the contributions from different skills and professional competences can optimize the management of PMA, and take the best advantage of available human and material resources. Another important point is the need to implement adequate training plans for the appropriate management of agitated patients; this should be addressed with regard to all the professionals involved. Adequate training and continuing education, along with mutual discussion and assessment of results, are the only ways by which constant improvement in the services can be achieved. Finally, the time has probably come to start thinking about the creation of Diagnostic, Therapeutic and Care Pathways (DTCP) specifically developed for PMA, which would contribute to making the overall management of this condition more homogeneous and structured.

To achieve these goals, it is essential to build a proper culture and attitude among health care profession-

als, and to make a great logistic and organizational effort, especially with regard to hospital emergency facilities.

Conclusions

Psychomotor agitation is a common condition that may be associated with a variety of psychiatric and medical illnesses. Its manifestations go along a continuum that ranges from a situation of simple ideational activation to the most acute and violent episodes. If not adequately treated, PMA can rapidly escalate to the highest levels of severity. Therefore, it is essential to treat agitation at an early stage, adopting an approach that is ethical, non-invasive, respectful of the patient's dignity and oriented to the creation of a good "therapeutic alliance" with the physician, thus avoiding the stigma that too often accompanies psychiatric patients.

Except in the case of imminent and serious danger for the safety of the people involved, the first therapeutic step should always be verbal de-escalation. If this is not successful or not indicated, the main classes of medications commonly used in PMA are FGAs, SGAs and benzodiazepines, which are all available in oral, parenteral and – for loxapine – inhaled formulations. The selection of medication to be used in individual patients mainly depends on the underlying disease that is causing PMA, but generally current guidelines recommend SGAs over FGAs (if an antipsychotic is indicated) and oral or inhaled formulations over parenteral ones. Coercive measures (restraint and seclusion) should be avoided whenever possible, limiting their use to cases in which they are absolutely necessary and only for the time that is strictly needed. In real-life clinical practice, the assessment and management of agitation depend on whether or not a patient is already known to psychiatric services, on the setting in which care is delivered (patient's home, community facilities, emergency department, hospital), and on the severity of PMA (mild, moderate or severe). In all cases that require fast, effective and safe therapeutic action, inhaled loxapine is a valuable option.

In order to continuously improve the clinical management of PMA, an effort should be made to start treatment as early as possible, identifying patients at an earlier stage of their continuum and favoring the network of community facilities over the hospital setting. A multidisciplinary clinical approach, appropriate training of health care staff and a research effort to identify predictors of PMA are further aspects of central importance.

Take home messages for psychiatric care

- Psychomotor agitation (PMA) is a common condition that may be associated with a wide range of psychiatric and medical illnesses conditions
- Symptoms go along a continuum that ranges from simple ideational activation to the most acute and violent manifestations
- If not adequately treated, PMA can rapidly escalate up to the highest levels of severity
- It is essential to treat PMA at an early stage, thus preventing symptom escalation, and allowing the adoption of an ethical, non-invasive, respectful approach, and avoiding patient stigmatization
- Except in the case of imminent and serious danger for safety, the first therapeutic step should always be verbal de-escalation
- The main classes of medications commonly used in PMA are first- and second-generation antipsychotics and benzodiazepines
- The selection of medication to be used mainly depends on the underlying disease that is causing PMA; when an antipsychotic is indicated, second-generation drugs are preferred over first-generation drugs
- For pharmacological therapy, non-invasive options such as oral and inhaled formulations are preferred over invasive treatments
- Coercive measures (restraint and seclusion) should be avoided whenever possible, considering them a last resort in cases of extreme necessity
- In real-life clinical practice, the assessment and management of PMA depend on whether or not a patient is already known to psychiatric services, on the setting in which care is delivered, and on the level of agitation (mild, moderate or severe)
- Earlier treatment, involvement of community psychiatric facilities, continuing education of health care personnel, a multidisciplinary approach, and research on predictors of PMA are desirable goals for the future

References

1 Marder SR. *A review of agitation in mental illness: treatment guidelines and current therapies.* J Clin Psychiatry 2006;67(Suppl 10):13-21.

2 Citrome L. *Atypical antipsychotics for acute agitation. New intramuscular options offer advantages.* Postgrad Med 2002;112:85-8.

3 Battaglia J. *Pharmacological management of acute agitation.* Drugs 2005;65:1207-22.

4 Allen MH, Currier GW, Carpenter D, et al; Expert Consensus Panel for Behavioral Emergencies 2005. *The expert consensus guideline series. Treatment of behavioral emergencies 2005.* J Psychiatr Pract 2005;11(Suppl 1):5-108.

5 Zeller SL, Rhoades RW. *Systematic reviews of assessment measures and pharmacologic treatments for agitation.* Clin Ther 2010;32:403-25.

6 Nordstrom K, Allen MH. *Managing the acutely agitated and psychotic patient.* CNS Spectr 2007;12(10 Suppl 17):5-11.

7 Nordstrom K, Zun LS, Wilson MP, et al. *Medical evaluation and triage of the agitated patient: consensus statement of the American Association for Emergency Psychiatry project Beta medical evaluation workgroup.* West J Emerg Med 2012;13:3-10.

8 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).* Washington, DC 2013.

9 Lindenmayer JP. *The pathophysiology of agitation.* J Clin Psychiatry 2000;61(Suppl 14):5-10.

10 Stowell KR, Florence P, Harman HJ, et al. *Psychiatric evaluation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA Psychiatric Evaluation Workgroup.* West J Emerg Med 2012;13:11-6.

11 Citrome L, Volavka J. *Violent patients in the emergency setting.* Psychiatr Clin North Am 1999;22:789-801.

12 Hankin CS, Bronstone A, Koran LM. *Agitation in the inpatient psychiatric setting: a review of clinical presentation, burden, and treatment.* J Psychiatr Pract 2011;17:170-85.

13 Citrome L. *Addressing the need for rapid treatment of agitation in schizophrenia and bipolar disorder: focus on inhaled loxapine as an alternative to injectable agents.* Ther Clin Risk Manag 2013;9:235-45.

14 Allen MH. *Managing the agitated psychotic patient: a reappraisal of the evidence.* J Clin Psychiatry 2000;61(Suppl 14):11-20.

15 Di Florio A, Craddock N, van den Bree M. *Alcohol misuse in bipolar disorder. A systematic review and meta-analysis of comorbidity rates.* Eur Psychiatry 2014;29:117-24.

16 Rounsaville BJ. *DSM-V research agenda: substance abuse/psychosis comorbidity.* Schizophr Bull 2007;33:947-52.

17 Sara GE, Large MM, Matheson SL, et al. *Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation.* Aust N Z J Psychiatry 2015;49:106-17.

18 Jordaan GP, Emsley R. *Alcohol-induced psychotic disorder: a review.* Metab Brain Dis 2014;29:231-43.

19 Sachs GS. *A review of agitation in mental illness: burden of illness and underlying pathology.* J Clin Psychiatry 2006;67(Suppl 10):5-12.

20 Cots F, Chiarello P, Pérez V, et al. *Hospital costs associated with agitation in the acute care setting.* Psychiatr Serv 2016;67:124-7.

21 Wittchen HU, Jacobi F, Rehm J, et al. *The size and burden of mental disorders and other disorders of the brain in Europe 2010.* Eur Neuropsychopharmacol 2011;21:655-79.

22 Becerra V, Gómez-Ulloa D, Garrido E, et al. *Agitación: aproximación a la epidemiología y manejo clínico en España según expertos.* Presented at the XXXIII Jornadas de Economía de la Salud, Santander, Spain, June 18-21, 2013: poster P-081.

23 Pascual JC, Madre M, Puigdemont D, et al. *A naturalistic study: 100 consecutive episodes of acute agitation in a psychiatric emergency department.* Actas Esp Psiquiatr 2006;34:239-44.

24 Tardiff K, Sweillam A. *Assaultive behavior among chronic inpatients.* Am J Psychiatry 1982;139:212-15.

25 Huf G, Alexander J, Allen MH. *Haloperidol plus promethazine for psychosis induced aggression.* Cochrane Database Syst Rev 2005;(1):CD005146.

26 Oliva-Moreno J, López-Bastida J, Osuna-Guerrero R, et al. *The costs of schizophrenia in Spain.* Eur J Health Econ 2006;7:182-8.

27 Hazlett SB, McCarthy ML, Londner MS, et al. *Epidemiology of adult psychiatric visits to US emergency departments.* Acad Emerg Med 2004;11:193-5.

28 Allen MH, Currier GW. *Use of restraints and pharmacotherapy in academic psychiatric emergency services.* Gen Hosp Psychiatry 2004;26:42-9.

29 Marco CA, Vaughan J. *Emergency management of agitation in schizophrenia.* Am J Emerg Med 2005;23:767-76.

30 Hazlett EA, Buchsbaum MS, Kemether E, et al. *Abnormal glucose metabolism in the mediodorsal nucleus of the thalamus in schizophrenia.* Am J Psychiatry 2004;161:305-14.

31 Orta J, Riesgo Y, Vieitez P, et al. *Prevalence of agitation-hostility during acute episodes in patients with schizophrenia.* Presented at the 15th European Congress of Psychiatry, Madrid, Spain, March 17-21, 2007.

32 Sacchetti E. Presented at the 2016 Brixia International Conference, Brescia, Italy, June 9-11, 2016.

33 Perugi G, Akiskal HS, Micheli C, et al. *Clinical characterization of depressive mixed state in bipolar-I patients: Pisa-San Diego collaboration.* J Affect Disord 2001;67:105-14.

34 Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. *The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders.* Am J Psychiatry 2013;170:1249-62.

35 Perugi G, Angst J, Azorin JM, et al; BRIDGE-II-Mix Study Group. *Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study.* J Clin Psychiatry 2015;76:e351-58.

36 Maj R, Pirozzi R, Magliano L, Bartoli L. *Agitated depression in bipolar I disorder: prevalence, phenomenology, and outcome.* Am J Psychiatry 2003;160:2134-40.

37 Koukopoulos A, Pani L, Serra G, et al. *La dépression anxieuse-excitée: un syndrome affectif mixte.* Encephale 1995;21(special number 6):33-6.

38 Spitzer RL, Endicott J, Robins E. *Research diagnostic criteria: rationale and reliability.* Arch Gen Psychiatry 1978;35:773-82.

39 Serretti A, Olgiati P. *Profiles of "manic" symptoms in bipolar I, bipolar II and major depressive disorders.* J Affect Disord 2005;84:159-66.

40 Goodwin FK, Jamison KR. *Manic-Depressive Illness.* New York: Oxford University Press 1990.

41 Keck PE Jr, McElroy SL, Arnold LM. *Bipolar disorder.* Med Clin North Am 2001;85:645-61.

42 Iwanami T, Maeshima H, Baba H, et al. *Psychomotor agitation in major depressive disorder is a predictive factor of mood-switching.* J Affect Disord 2015;170:185-9.

43 Angst J, Gamma A, Benazzi F, et al. *Does psychomotor agitation in major depressive episodes indicate bipolarity? Evidence from the Zurich Study.* Eur Arch Psychiatry Clin Neurosci 2009;259:55-63.

44 Bartels SJ, Horn SD, Smout RJ, et al. *Agitation and depression in frail nursing home elderly patients with dementia:*

treatment characteristics and service use. Am J Geriatr Psychiatry 2003;11:231-8.
45 Srikanth S, Nagaraja AV, Ratnavalli E. *Neuropsychiatric symptoms in dementia-frequency, relationship to dementia severity and comparison in Alzheimer's disease, vascular dementia and frontotemporal dementia.* J Neurol Sci 2005;236:43-8.
46 Devanand DP, Jacobs DM, Tang MX, et al. *The course of psychopathologic features in mild to moderate Alzheimer disease.* Arch Gen Psychiatry 1997;54:257-63.
47 Citrome L. *Agitation III: Pharmacologic treatment of agitation.* In: Glick RL, Berlin AB, Fishkind AB, et al. (Eds.). *Emergency psychiatry. Principles and practice*. Philadelphia, Pa: Wolters Kluwer Health/Lippincott Williams & Wilkins 2008, pp. 137-47.
48 Hankin CS, Bronstone A, Zun L. *Estimated United States incidence of physical assaults perpetrated by agitated adult patients with schizophrenia or bipolar disorder on nurses and physicians in the general emergency department*. Poster presented at the American Society for Health-System Pharmacists 2010 Summer Meeting, Tampa, FL, June 6-9, 2010.
49 Nijman HL, Palmstierna T, Almvik R, et al. *Fifteen years of research with the Staff Observation Aggression Scale: a review.* Acta Psychiatr Scand 2005;111:12-21.
50 National Institute for Health and Clinical Excellence (NICE). *Violence: the short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments.* London: NICE 2005.
51 Dean K, Walsh E, Morgan C, et al. *Aggressive behaviour at first contact with services: findings from the AESOP First Episode Psychosis Study.* Psychol Med 2007;37:547-57.
52 Binder RL, McNiel DE. *Effects of diagnosis and context on dangerousness.* Am J Psychiatry 1988;145:728-32.
53 Peiró S, Gómez G, Navarro M, et al; Psychosp Group. *Length of stay and antipsychotic treatment costs of patients with acute psychosis admitted to hospital in Spain. Description and associated factors. The Psychosp study.* Soc Psychiatry Psychiatr Epidemiol 2004;39:507-13.
54 Pilowski LS, Ring H, Shine PJ, et al. *Rapid tranquillisation. A survey of emergency prescribing in a general psychiatric hospital.* Br J Psychiatry 1992;160:831-35.
55 Grassi L, Biancosino B, Marmai L, et al. *Violence in psychiatric units. A 7-years Italian study of persistently assaultive patients.* Soc Psychiatry Psychiatr Epidemiol 2006;41:698-703.
56 Biancosino B, Delmonte S, Grassi L, et al. *Violent behavior in acute psychiatric inpatient facilities. A national survey in Italy.* J Nerv Ment Dis 2009;197:772-82.
57 Soyka M, Ufer S. *Aggressiveness in schizophrenia: prevalence, psychopathological and sociodemographic correlates.* Fortschr Neurol Psychiatr 2002;70:171-7.
58 Tanke ED, Yesavage JA. *Characteristics of assaultive patients who do and do not provide visible cues of potential violence.* Am J Psychiatry 1985;142:1409-13.
59 Walsh E, Buchanan A, Fahy T. *Violence and schizophrenia: examining the evidence.* Br J Psychiatry 2002;180:490-5.
60 Humphreys MS, Johnstone EC, MacMillan JF, et al. *Dangerous behaviour preceding first admissions for schizophrenia.* Br J Psychiatry 1992;161:501-5.
61 Volavka J, Laska E, Baker S, et al. *History of violent behaviour and schizophrenia in different cultures. Analyses based on the WHO study on determinants of outcome of severe mental disorders.* Br J Psychiatry 1997;171:9-14.
62 Monahan J, Appelbaum P. *Reducing violence risk: diagnostically based clues from the MacArthur Violence Risk Assessment Study*. In: Hodgins S (Ed.). *Effective Prevention of Crime and Violence among the Mentally Ill*. The Netherlands: Kluwer Academic Publishers 2000, pp. 19-34.
63 Swanson JW, Holzer CE 3rd, Ganju VK, et al. *Violence and psychiatric disorder in the community: evidence from the epidemiologic catchment area surveys.* Hosp Community Psychiatry 1990;41:761-70.
64 Hansberry MR, Chen E, Gorbien MJ. *Dementia and elder abuse.* Clin Geriatr Med 2005;21:315-32.
65 Gray KF. *Managing agitation and difficult behavior in dementia.* Clin Geriatr Med 2004;20:69-82.
66 Chen JC, Borson S, Scanlan JM. *Stage-specific prevalence of behavioral symptoms in Alzheimer's disease in a multi-ethnic community sample.* Am J Geriatr Psychiatry 2000;8:123-33.
67 Jaffe A, Levine J, Citrome L. *"Stat" medication administration predicts hospital discharge.* Psychiatr Q 2009;80:65-73.
68 Barlow K, Grenyer B, Ilkiw-Lavalle O. *Prevalence and precipitants of aggression in psychiatric inpatient units.* Aust N Z J Psychiatry 2000;34:967-74.
69 Carr VJ, Lewin TJ, Sly KA, et al. *Adverse incidents in acute psychiatric inpatient units: rates, correlates and pressures.* Aust N Z J Psychiatry 2008;42:267-82.
70 Steinert T, Wiebe C, Gebhardt RP. *Aggressive behavior against self and others among first-admission patients with schizophrenia.* Psychiatr Serv 1999;50:85-90.
71 Mellesdal L. *Aggression on a psychiatric acute ward: a three-year prospective study.* Psychol Rep 2003;92:1229-48.
72 Rubio-Valera M, Luciano JV, Ortiz JM, et al. *Health service use and costs associated with aggressiveness or agitation and containment in adult psychiatric care: a systematic review of the evidence.* BMC Psychiatry 2015;15:35.
73 Flood C, Bowers L, Parkin D. *Estimating the costs of conflict and containment on adult acute inpatient psychiatric wards.* Nurs Econ 2008;26:325-30.
74 Garrido Viñado E, Lizano-Díez I, Roset Arissó PN, et al. *El coste económico de los procedimientos de contención mecánica de origen psiquiátrico en España.* Psiq Biol 2015;22:12-6.
75 Olshaker JS, Browne B, Jerrard DA, et al. *Medical clearance and screening of psychiatric patients in the emergency department.* Acad Emerg Med 1997;4:124-8.
76 Ciurli P, Formisano R, Bivona U, et al. *Neuropsychiatric disorders in persons with severe traumatic brain injury: prevalence, phenomenology, and relationship with demographic, clinical, and functional features.* J Head Trauma Rehabil 2011;26:116-26.
77 Sarkari NB, Thacker AK, Barthwal SP, et al. *Japanese encephalitis (JE). Part I: clinical profile of 1,282 adult acute cases of four epidemics.* J Neurol 2012;259:47-57.
78 Harris RL, Musher DM, Bloom K, et al. *Manifestations of sepsis.* Arch Intern Med 1987;147:1895-906.
79 Khurana V, Gambhir IS, Kishore D. *Evaluation of delirium in elderly: a hospital-based study.* Geriatr Gerontol Int 2011;11:467-73.
80 Caplan LR. *Delirium: a neurologist's view – the neurology of agitation and overactivity.* Rev Neurol Dis 2010;7:111-8.
81 *Acute poisoning following ingestion of medicines: initial management. How to treat life-threatening complications and to evaluate the risk of delayed effects and psychological distress.* Prescrire Int 2010;19:284-91.
82 Bahn RS, Burch HB, Cooper DS, et al; American Thyroid Association; American Association of Clinical Endocrinologists. *Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists.* Endocr Pract 2011;17:456-520.
83 Lambrey S, Adam C, Baulac M, et al. *Postictal psychosis syndrome: a clinical entity to be recognized [article in French].* Rev Neurol (Paris) 2009;165:155-63.

[84] Gurrera RJ, Caroff SN, Cohen A, et al. *An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method.* J Clin Psychiatry 2011;72:1222-8.

[85] Poeschla BD, Bartle P, Hansen KP. *Serotonin syndrome associated with polypharmacy in the elderly.* Gen Hosp Psychiatry 2011;33:301.e9-11.

[86] Saitz R. *Introduction to alcohol withdrawal.* Alcohol Health Res World 1998;22:5-12.

[87] Folstein MF, Folstein SE, McHugh PR. *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res 1975;12:189-98.

[88] Cipriani A, Barbui C, Salanti G, et al. *Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis.* Lancet 2011;378:1306-15.

[89] Rynn MA, Brawman-Mintzer O. *Generalized anxiety disorder: acute and chronic treatment.* CNS Spectr 2004;9:716-23.

[90] Richmond JS, Berlin JS, Fishkind AB, et al. *Verbal de-escalation of the agitated patient: consensus statement of the American Association for Emergency Psychiatry Project BETA De-escalation Workgroup.* West J Emerg Med 2012;13:17-25.

[91] Meythaler JM, Peduzzi JD, Eleftheriou E, et al. *Current concepts: diffuse axonal injury-associated traumatic brain injury.* Arch Phys Med Rehabil 2001;82:1461-71.

[92] Kaufman DM, Zun L. *A quantifiable, Brief Mental Status Examination for emergency patients.* J Emerg Med 1995;13:449-56.

[93] Lidz CW, Mulvey EP, Gardner W. *The accuracy of predictions of violence to others.* JAMA 1993;269:1007-11.

[94] Jacobs DG, Baldessarini RJ, Conwell Y, et al. *Practice guideline for the assessment and treatment of patients with suicidal behaviors*. American Psychiatric Association 2003. Available online at: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide.pdf (last accessed: 30/06/2016).

[95] Corrigan JD. *Development of a scale for assessment of agitation following traumatic brain injury.* J Clin Exp Neuropsychol 1989;11:261-77.

[96] Zun LS, Downey LV. *Level of agitation of psychiatric patients presenting to an emergency department.* Prim Care Companion J Clin Psychiatry 2008;10:108-13.

[97] Bogner JA, Corrigan JD, Fugate L, et al. *Role of agitation in prediction of outcomes after traumatic brain injury.* Am J Phys Med Rehabil 2001;80:636-44.

[98] Cohen-Mansfield J, Marx MS, Rosenthal AS. *A description of agitation in a nursing home.* J Gerontol 1989;44:M77-84.

[99] Shah A, Evans H, Parkash N. *Evaluation of three aggression/agitation behaviour rating scales for use on an acute admission and assessment psychogeriatric ward.* Int J Geriatr Psychiatry 1998;13:415-20.

[100] Finkel SI, Lyons JS, Anderson RL. *A brief agitation rating scale (BARS) for nursing home elderly.* J Am Geriatr Soc 1993;41:50-2.

[101] Lasalvia A, Bonetto C, Cristofalo D, et al. *Predicting clinical and social outcome of patients attending 'real world' mental health services: a 6-year multi-wave follow-up study.* Acta Psychiatr Scand Suppl 2007;(437):16-30.

[102] Yudofsky SC, Kopecky HJ, Kunik M, et al. *The Overt Agitation Severity Scale for the objective rating of agitation.* J Neuropsychiatry Clin Neurosci 1997;9:541-8.

[103] Kopecky HJ, Kopecky CR, Yudofsky SC. *Reliability and validity of the Overt Agitation Severity Scale in adult psychiatric inpatients.* Psychiatr Q 1998;69:301-23.

[104] Kay SR, Fiszbein A, Opler LA. *The positive and negative syndrome scale (PANSS) for schizophrenia.* Schizophr Bull 1987;13:261-76.

[105] Kay SR, Sevy S. *Pyramidical model of schizophrenia.* Schizophr Bull 1990;16:537-45.

[106] Breier A, Meehan K, Birkett M, et al. *A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia.* Arch Gen Psychiatry 2002;59:441-8.

[107] Sachs GS, Gaulin BD, Gutierrez-Esteinou R, et al. *Antimanic response to aripiprazole in bipolar I disorder patients is independent of the agitation level at baseline.* J Clin Psychiatry 2007;68:1377-83.

[108] Marder SR, West B, Lau GS, et al. *Aripiprazole effects in patients with acute schizophrenia experiencing higher or lower agitation: a post hoc analysis of 4 randomized, placebo-controlled clinical trials.* J Clin Psychiatry 2007;68:662-8.

[109] Lesem MD, Tran-Johnson TK, Riesenberg RA, et al. *Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine.* Br J Psychiatry 2011;198:51-8.

[110] Montoya A, Valladares A, Lizán L, et al. *Validation of the Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC) in a naturalistic sample of 278 patients with acute psychosis and agitation in a psychiatric emergency room.* Health Qual Life Outcomes 2011;9:18.

[111] Baker RW, Kinon BJ, Maguire GA, et al. *Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation.* J Clin Psychopharmacol 2003;23:342-8.

[112] Currier GW, Citrome LL, Zimbroff DL, et al. *Intramuscular aripiprazole in the control of agitation.* J Psychiatr Pract 2007;13:159-69.

[113] Chaichan W. *Evaluation of the use of the positive and negative syndrome scale-excited component as a criterion for administration of p.r.n. medication.* J Psychiatr Pract 2008;14:105-13.

[114] Guy W. *ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication, revised ed.* Rockville, MD: National Institute of Mental Health 1976: pp 218-222.

[115] Vanier M, Mazaux JM, Lambert J, et al. *Assessment of neuropsychologic impairments after head injury: interrater reliability and factorial and criterion validity of the Neurobehavioral Rating Scale-Revised.* Arch Phys Med Rehabil 2000;81:796-806.

[116] McCauley SR, Levin HS, Vanier M, et al. *The neurobehavioural rating scale-revised: sensitivity and validity in closed head injury assessment.* J Neurol Neurosurg Psychiatry 2001;71:643-51.

[117] Yudofsky SC, Silver JM, Jackson W, et al. *The Overt Aggression Scale for the objective rating of verbal and physical aggression.* Am J Psychiatry 1986;143:35-9.

[118] Kay SR, Wolkenfeld F, Murrill LM. *Profiles of aggression among psychiatric patients. I. Nature and prevalence.* J Nerv Ment Dis 1988;176:539-46.

[119] Kavoussi RJ, Coccaro EF. *Divalproex sodium for impulsive aggressive behavior in patients with personality disorder.* J Clin Psychiatry 1998;59:676-80.

[120] Armenteros JL, Lewis JE. *Citalopram treatment for impulsive aggression in children and adolescents: an open pilot study.* J Am Acad Child Adolesc Psychiatry 2002;41:522-9.

[121] Mischoulon D, Dougherty DD, Bottonari KA, et al. *An open pilot study of nefazodone in depression with anger attacks: relationship between clinical response and receptor binding.* Psychiatry Res 2002;116:151-61.

[122] Cai G, Li T, Deng H, et al. *Affected sibling pair linkage analysis of qualitative and quantitative traits for schizophrenia on chromosome 22 in a Chinese population.* Am J Med Genet 2001;105:321-7.

[123] Margari F, Matarazzo R, Casacchia M; EPICA Study Group. *Italian validation of MOAS and NOSIE: a useful package for psychiatric assessment and monitoring of aggressive behaviours.* Int J Methods Psychiatr Res 2005;14:109-18.

[124] Perlman CM, Hirdes JP. *The aggressive behavior scale: a new scale to measure aggression based on the minimum data set.* J Am Geriatr Soc 2008;56:2298-303.

[125] Huber CG, Lambert M, Naber D, et al. *Validation of a Clinical Global Impression Scale for Aggression (CGI-A) in a sample of 558 psychiatric patients.* Schizophr Res 2008;100:342-8.

[126] Almvik R, Woods P, Rasmussen K. *The Brøset Violence Checklist. Sensitivity, specificity, and interrater reliability.* J Interpers Violence 2000;15:1284-96.

[127] McNiel DE, Binder RL. *Screening for risk of inpatient violence.* Law Hum Behav 1994;18:579-86.

[128] Webster CD, Eaves D, Douglas KS, et al. *The HCR-20 scheme: the assessment of dangerousness and risk.* Burnaby, Canada: Simon Fraser University and Forensic Psychiatric Services Commission of British Columbia 1995.

[129] Douglas KS, Hart SD, Webster CD, et al. *Historical-Clinical-Risk Management-20, Version 3 (HCR-20^{V3}): development and overview.* Int J Forensic Ment Health 2014;13:93-108.

[130] Perkins DO. *Predictors of noncompliance in patients with schizophrenia.* J Clin Psychiatry 2002;63:1121-8.

[131] Amore M, Menchetti M, Tonti C, et al. *Predictors of violent behavior among acute psychiatric patients: clinical study.* Psychiatry Clin Neurosci 2008;62:247-55.

[132] Haim R, Rabinowitz J, Lereya J, et al. *Predictions made by psychiatrists and psychiatric nurses of violence by patients.* Psychiatr Serv 2002;53:622-4.

[133] Comitato Nazionale per la Bioetica. *La contenzione: problemi etici*. Presidenza del Consiglio dei Ministri, 23 aprile 2015. Available at: http://presidenza.governo.it/bioetica/pareri_abstract/La%20contenzione%20problemi%20bioetici.pdf (last accessed: 30/06/2016).

[134] Legge 13 maggio 1978, n. 180: "Accertamenti e trattamenti sanitari volontari e obbligatori". Published on the Gazzetta Ufficiale della Repubblica Italiana, May 16, 1978, n. 133. Available online at: http://www.salute.gov.it/imgs/C_17_normativa_888_allegato.pdf (last accessed: 30/06/2016).

[135] Garriga M, Pacchiarotti I, Kasper S, et al. *Assessment and management of agitation in psychiatry: expert consensus.* World J Biol Psychiatry 2016;17:86-128.

[136] National Collaborating Centre for Mental Health, commissioned by the National Institute for Health and Care Excellence. *Violence and aggression: short-term management in mental health, health and community settings: updated edition.* London: British Psychological Society 2015.

[137] Battaglia J, Lindborg SR, Alaka K, et al. *Calming versus sedative effects of intramuscular olanzapine in agitated patients.* Am J Emerg Med 2003;21:192-8.

[138] Wilson MP, Pepper D, Currier GW, et al. *The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry project Beta psychopharmacology workgroup.* West J Emerg Med 2012;13:26-34.

[139] Allen MH, Currier GW, Hughes DH, et al. *Treatment of behavioral emergencies: a summary of the expert consensus guidelines.* J Psychiatr Pract 2003;9:16-38.

[140] Zimbroff DL, Marcus RN, Manos G, et al. *Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole.* J Clin Psychopharmacol 2007;27:171-6.

[141] Battaglia J, Moss S, Rush J, et al. *Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study.* Am J Emerg Med 1997;15:335-40.

[142] Huf G, Alexander J, Allen MH. *Haloperidol plus promethazine for psychosis induced aggression.* Cochrane Database Syst Rev 2009;(3):CD005146.

[143] Lambert M, Schimmelmann BG, Karow A, et al. *Subjective well-being and initial dysphoric reaction under antipsychotic drugs – concepts, measurement and clinical relevance.* Pharmacopsychiatry 2003;36(Suppl 3):S181-90.

[144] Karow A, Schnedler D, Naber D. *What would the patient choose? Subjective comparison of atypical and typical neuroleptics.* Pharmacopsychiatry 2006;39:47-51.

[145] Popovic D, Nuss P, Vieta E. *Revisiting loxapine: a systematic review.* Ann Gen Psychiatry 2015;14:15.

[146] Citrome L. *New treatments for agitation.* Psychiatr Q 2004;75:197-213.

[147] Citrome L. *Inhaled loxapine for agitation revisited: focus on effect sizes from 2 Phase III randomised controlled trials in persons with schizophrenia or bipolar disorder.* Int J Clin Pract 2012;66:318-25.

[148] Allen MH, Feifel D, Lesem MD, et al. *Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial.* J Clin Psychiatry 2011;72:1313-21.

[149] Kwentus J, Riesenberg RA, Marandi M, et al. *Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine.* Bipolar Disord 2012;14:31-40.

[150] Dolder CR, Jeste DV. *Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high risk patients.* Biol Psychiatry 2003;53:1142-5.

[151] Kane JM. *Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence.* J Clin Psychiatry 2004;65(Suppl 9):16-20.

[152] Correll CU, Schenk EM. *Tardive dyskinesia and new antipsychotics.* Curr Opin Psychiatry 2008;21:151-6.

[153] Citrome L. *Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety.* J Clin Psychiatry 2007;68:1876-85.

[154] Shoptaw SJ, Kao U, Ling W. *Treatment for amphetamine psychosis.* Cochrane Database Syst Rev 2009;(1):CD003026.

[155] Ng AT, Zeller SL, Rhoades RW. *Clinical challenges in the pharmacologic management of agitation.* Prim Psychiatry 2010;17:46-52.

[156] Pratts M, Citrome L, Grant W, et al. *A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation.* Acta Psychiatr Scand 2014;130:61-8.

[157] Allen MH, Debanné M, Lazignac C, et al. *Effect of nicotine replacement therapy on agitation in smokers with schizophrenia: a double-blind, randomized, placebo-controlled study.* Am J Psychiatry 2011;168:395-9.

[158] Department of Health and Human Services. *Condition of participation: patient's rights.* Federal Register 482.13. 2006; 71426-71428.

[159] Knox DK, Holloman GH Jr. *Use and avoidance of seclusion and restraint: consensus statement of the American Association for Emergency Psychiatry project Beta seclusion and restraint workgroup.* West J Emerg Med 2012;13:35-40.

[160] Sailas E, Fenton M. *Seclusion and restraint for people with serious mental illnesses.* Cochrane Database Syst Rev 2000;(2):CD001163.

[161] Katsakou C, Bowers L, Amos T, et al. *Coercion and treatment satisfaction among involuntary patients.* Psychiatr Serv 2010;61:286-92.

[162] Currier GW, Walsh P, Lawrence D. *Physical restraints in the emergency department and attendance at subsequent outpatient psychiatric treatment.* J Psychiatr Pract 2011;17:387-93.

[163] Glick RL, Berlin JS, Fishkind AB, et al. *Emergency psychiatry. Principles and practice.* Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins 2008.

CANNABIS CONSUMPTION AND THE RISK OF PSYCHOSIS

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Summary

Objectives: Cannabis is the most widely used illicit drug globally and its use has been linked to an increased risk for psychotic disorders. An association between cannabis consumption and psychotic symptoms was consistently reported by several studies. This case-control study aimed to widen the current findings about the impact of cannabis exposure on the risk of psychosis, by investigating the pattern of cannabis consumption in a sample of first-episode of psychosis (FEP) patients compared to healthy controls.

Material and methods: 68 individuals who presented for the first time to mental health services of Palermo (Italy) with an ICD-10 diagnosis of psychotic disorders and 74 healthy were enrolled as part of the Sicilian Genetics and Psychosis study. Psychopathological assessment and diagnosis were carried out by the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). Socio-demographic data were collected by the modified version of the Medical Research Council (MRC) socio-demographic scale. All participants were interviewed using the Cannabis Experience Questionnaire – Modified Version to obtain a detailed assessment of lifetime patterns of cannabis and other illicit drug consumption. Logistic regression was applied to investigate the relationships between various aspects of cannabis use (lifetime use, age at first use, duration, and frequency of use) and case-control status while controlling for potential confounders.

Results: Patients started cannabis consumption about 3 years earlier than the control group (t = 3.1, p = 0.002) and were 8 times more likely to having started using cannabis before 15 years (adjusted OR = 8.0, 95% CI 2.4-27) than controls. Furthermore cases were more likely to smoke more frequently than controls (adjusted OR = 4.4, 95% CI 1.08-18). We did not find a difference in duration of cannabis use between cases and controls.

Conclusions: The findings suggest that cannabis exposure, and especially daily cannabis consumption, is associated with the risk for psychosis; however, the retrospective study design does not allow drawing firm conclusions about causality.

Key words: cannabis, schizophrenia, psychosis, tetrahydrocannabinol, drug and schizophrenia

Introduction

Cannabis exposure has been associated to an increased risk of developing psychosis. Cannabis is the most popular illicit drug worldwide, and although most people who smoke cannabis do not become psychotic, evidence from the literature supports an association between cannabis use and an increased risk of developing a psychotic disorder [1,2].

The main psychoactive component, which is responsible of the psychotogenic effect of cannabis, is Δ9-tetrahydrocannabinol (Δ9-THC). The other main constituent of cannabis is cannabidiol (CBD) which has antianxiety and antipsychotic properties [3,4]. Recently, high potency varieties of cannabis, such as "skunk" (*sensimilla*), have become available in the market over much of Europe. Such varieties of cannabis contain a high concentration of THC and a lower proportion of CBD which seems

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to "balance" the psychotogenic effect of the former [3 4]. Cannabis intoxication can cause brief psychotic episodes or may exacerbate pre-existing psychotic symptoms [5 6]. It has been shown that healthy people who are administered THC intravenously were more likely to develop transient psychotic-like experiences and that THC worsens psychotic symptoms in people suffering from psychosis [7]. THC exerts its psychotogenic role by modulating the dopamine neurotransmission, which is involved in development of psychotic symptoms.

The first report suggesting that cannabis might be a risk factor for psychosis was the Swedish Conscript study. This was a 15 year follow-up of a cohort of 45.570 conscripts into the armed forces. The risk of schizophrenia was 2.3 fold higher among subjects who had used cannabis by 18 years and there was a dose response relationship, as the risk of developing schizophrenia was even higher in those who had smoked cannabis more frequently [8]. Subsequently, a series of cohort studies have shown that cannabis use generally predates psychosis [9-13]. For instance, the Dunedin cohort study reported that children and adolescents who had used cannabis by the age of 15 years were 4.5 times more likely to develop schizophreniform psychosis at the age of 26 years [9]. van Os et al. reported a three times higher risk of developing psychotic symptoms in the general population associated to cannabis consumption [12]. Two meta-analyses concluded that cannabis consumption was associated with approximately two-fold increased risk of developing a psychotic disorder [1 2].

Individuals who showed any evidence of psychosis proneness appear especially vulnerable, as those who started using cannabis in early adolescence. A meta-analysis by Large et al. supported the association between cannabis consumption and an earlier age at first presentation of psychosis [14]. Other studies confirmed that cannabis use is associated to an earlier age at first presentation of schizophrenia and that there is an interaction between cannabis use and gender difference in age at first presentation, in the way that the difference by gender in age at first presentation is reduced in cannabis users [15]. Furthermore, recent evidence shows that high potency cannabis and higher frequency of use are associated with a higher risk of developing psychosis [3].

However, only a small proportion of cannabis users develop psychotic symptoms or schizophrenia. Cannabis users who develop psychosis may have an underlying genetic susceptibility, and some gene polymorphisms have been associated to an increased risk to develop psychosis [16-21]; nevertheless, these results need to be further replicated.

Materials and methods

The Sicilian Genetic and Psychosis (SGAP) study is an incidence and a case-control study, carried on by the Psychiatric Section of Palermo University Department of Experimental Biomedicine and Clinical Neurosciences (BioNeC), aimed at identifying the role of putative genetic and environmental risk factors for psychosis, including cannabis.

In this work the focus will be on the impact of cannabis exposure on the risk of psychoses. Specifically, we aimed to compare patterns of cannabis consumption between cases and controls (exposure to cannabis lifetime, age at first use, duration of cannabis consumption, total number of times used, frequency of use) and to discuss the impact of cannabis exposure on psychosis risk in Palermo.

Participants

A screening of cases aged between 18-65 years affected by any psychoses was run on all the subjects presenting to the mental health services of Palermo with a first-episode of psychosis (FEP) in a three-year period. 204 patients at their first-episode of psychosis (defined as the first contact with psychiatric services) were identified.

Inclusion criteria for cases were:

- presence of symptoms of any psychosis such as delusions, hallucinations, thought disorder, bizarre or disturbed behaviour, negative symptoms, mania;
- residence in Palermo;
- first ever contact with psychiatric services for psychotic symptoms;
- age between 18 and 65 years;
- absence of an organic cause of psychosis and severe learning disability;
- diagnosis of ICD-10 criteria for schizophrenia (F20), other non-affective psychoses (F21-29) or affective psychoses (F30-33).

Cases were excluded if they met any of the following criteria:

- presence of an organic cause underlying psychotic symptoms;
- previous contact with mental health services for an episode of psychosis;
- age under 18 or over 65;
- presence of psychotic symptoms resulting from acute intoxication as defined by ICD-10 criteria.

A case control analysis was performed in a subsample of 68 cases (out of the 204 identified for the incidence study) that were compared to 74 healthy controls. The control sample was recruited from the same catchment area as cases, through leaflet distributions and Internet and newspaper advertisements, and was representative of the general population at risk for the disease.

Measures

The assessment of cases was performed by the following instruments:

- the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) [22] was used to assess psychopathology and to define the diagnosis of psychosis;
- a modified version of the MRC Socio-demographic Schedule [23] adapted to the Italian context was used to collect socio-demographic data (age, gender, ethnicity, level of education, and occupational status);
- the Cannabis Experience Questionnaire – Modified Version (CEQmv) [3] was administered to collect data on cannabis and other illicit drugs consumption. The questionnaire explores cannabis consumption in details, including: age at first use, lifetime cannabis consumption, current cannabis consumption (defined as cannabis consumption within the four weeks before the assessment), frequency of use, duration of use in years (more or less than 5 years), other drugs consumption (including all illicit drugs, among which stimulants, tobacco, and alcohol).

Controls were administered the same instruments as cases except the SCAN and they were asked to complete the Psychosis Screening Questionnaire (PSQ) [24] to exclude the presence of a current or past psychotic disorder.

Ethics

The study was approved by the Ethical Committee of the Palermo University Medical School and the data collection in the mental health services has been authorized by the Department of Mental Health of Palermo which coordinates all the psychiatric services involved in the study. The work has been performed in accordance with the principles of the 1983 Declaration of Helsinki. Study participants were asked to sign a consent form before attending the interview.

Analyses

Patterns of cannabis use in cases and controls were investigated using, where appropriate, $\chi 2$-test or Fisher exact test (cannabis use lifetime, current cannabis use, frequency of cannabis use, use before and after 15 years). Welch test and Wilcoxon tests were used to calculate mean age at first use and mean duration of cannabis use for cases and controls because of unequal variances. ANOVA was used to evaluate differences in the mean age of first cannabis consumption by case-control status. Logistic regression was used to analyze the association between the pattern of cannabis use and the risk of psychosis, controlling for possible confounders. Confounders were selected as the main socio-demographic differences between cases and controls that might influence the risk of psychosis (age, gender, level of education, occupational status, psychiatric family history, and other drug use).

Results

Socio-demographic characteristics of cases and controls are displayed in Table I.

Table II summarizes differences in patterns of cannabis consumption between cases and controls. In Palermo sample, patients were not more likely than controls to have smoked cannabis at least once, lifetime (OR = 0.4, 95% CI 0.1-1.1) and this may reflect that cannabis consumption is quite spread in the general population. No differences in lifetime cannabis consumption by gender both in cases ($\chi 2 = 1.4$, df = 1, p = 0.238) and controls ($\chi 2 = .8$, df = 1, p = 0.178) were found.

After adjusting for possible confounders (age, gender, education, occupational status, psychiatric family history, and other drugs abuse) cases were over 5 times (adjusted OR = 5.4 ,95% CI 1.2-24.1) more likely than controls to be current cannabis consumers (meaning having smoked cannabis in the previous four weeks). In addition, mean age at first use of cannabis differed between cases and controls. Patients started cannabis consumption about 3 years earlier than controls (Welch test t = 3.1, df = 60, p = 0.002).

Accordingly to the existing literature, age of 15 years old might be a critical age of first exposure [25 26]; therefore, we investigated the odds of being a case having been exposed to cannabis “before 15 years of age”. We found that cases were 8 times more likely than controls to having started using cannabis before 15 years (adj. OR = 8, 95% CI 2.4-27).

Furthermore, previous literature on cannabis exposure in FEP patients reported that cases were about six times more likely than controls to use cannabis every day [3]. In Palermo sample, frequency of cannabis consumption in cannabis users was coded as

Table I. Sample characteristics of cases and controls.

	Cases (n = 68)	Controls (n = 74)	p*
Age, years mean (sd)	28.25 (11.2)	36 (13.2)	**< 0.001**
Median (IQR)	24 (13)	33.5 (28)	
No details	-	-	
Gender, n (%)			
Male	44 (64.7)	39 (52.7)	0.147
Female	24 (35.3)	35 (47.3)	
No details	-	-	
IQ (WAIS) mean (sd)	78.71 (16.81)	101.58 (23.05)	**< 0.001**
No details	34	-	
Migration status, n (%)			
Natives	60 (88.2)	70 (94.6)	0.174
Migrant	8 (11.8)	4 (5.4)	
No details	-	-	
Ethnicity, n (%)			
Caucasian	64 (94.1)	71 (95.95)	0.710
Non Caucasian	4 (5.9)	3 (4.05)	
No details	-	-	
Level of education, n (%)			
No education	0	2 (2.7)	**< 0.001**
Primary school	9 (13.4)	1 (1.4)	
Junior High	26 (38.8)	13 (17.8)	
Diploma	30 (44.8)	47 (64.4)	
University	2 (3)	10 (13.7)	
No details	1	1	
Mean age left education, sd	16 (2.91)	19.3 (3.5)	**< 0.001**
No details	1	1	
Employment, n (%)			
Unemployed	41 (61.2)	17 (23)	**< 0.001**
Employed	14 (20.9)	35 (47.3)	
Student	12 (17.9)	11 (14.9)	
Retired	0	11 (14.9)	
No details	1	-	
Relationship status, n (%)			
In a stable relationship	14 (20.6)	47 (63.5)	**< 0.001**
Single/separated/divorced	54 (79.4)	27 (36.5)	
No details	-	-	

** p value from χ_2 tests, Fisher's tests, t test, Wilcoxon test.*

"frequent" (e.g. everyday use and more than 3 times a week) and "sporadic" (meaning that the subject tried cannabis only once or twice lifetime, a few times each month and a few times each year). Cases who were cannabis consumers were more likely to smoke more frequently than controls (adj. OR = 4.4, 95% CI 1.08-18). Frequency of cannabis use was further analysed in terms of "daily use" as opposite to "less than daily use". Consistently with a previous study in an UK sample of FEP [3], in our sample cases were 7.5 times more likely to smoke cannabis everyday compared to controls ($\chi 2$ = 9.4, df = 1, p-value = 0.004; adj. OR = 7.5, 95% CI 1.9-29.7).

Moreover, we compared the total number of times that cases and controls had smoked cannabis lifetime ("up to 50 times" *versus* "between 50 and over 200 times") and we found that patients were more likely than controls to have used cannabis between 50 and over 200 times (adj. OR = 5.0, 95% CI 1.5-16.4).

We did not find a difference in duration of use of cannabis use between cases and controls. Mean duration of cannabis consumption was 7.4 years for cases and 6.8 years for controls (Welch test t = -0.3, df = 45, p = 0.785).

Table II. Patterns of cannabis use in cases and controls.

	Cases (n = 68)	Controls (n = 74)	p*
Cannabis use lifetime, n (%)			
Yes	29 (44.6)	42 (56.76)	0.153
No	36 (55.4)	32 (43.2)	
No details	3	0	
Current cannabis use* (at the time of the assessment), n (%)			
Yes	14 (51.85)	9 (21.4)	**0.009**
No†	13 (48.15)	33 (78.5)	
No details	2	0	
Frequency of cannabis use, n (%)			**0.003**
Everyday	12 (44.4)	4 (10.8)	
Less than everyday	15 (55.5)	33 (89.2)	
No details	2	5	
Total number of time used, n (%)			**0.011**
< 50 times	7 (27)	22 (59.46)	
> 50 and over 200	19 (73)	15 (40.54)	
No details	3	5	
Age of first use, mean (sd)	16 (2.34)	19 (5.37)	**0.002**
Mean duration cannabis, years, (sd)	7.4 (7)	6.8 (7.67)	**0.670**

**p value from χ_2 tests, Fisher's tests, t test, Wilcoxon test. †No current use was defined as no cannabis consumption in the previous 4 weeks as reported in the GAP study. The first row refers to all the sample of cases and controls while the following rows of the tables refer only to the subgroup of cannabis smokers in cases (n = 29) and controls (n = 42).*

Discussion

We found that in the Palermo sample lifetime cannabis exposure was similar in patients and in healthy controls. However, lifetime cannabis use does not say much about the extent of exposure to cannabis, since it is likely that some people only tried cannabis a few times in their life. A more significant index of cannabis exposure is cannabis consumption before the onset of psychosis; in this work we considered "cannabis consumption at the time of assessment". Cases were 5 times more likely than controls to be current users at the time of assessment, and this suggests that patients may have smoked more recently than healthy controls but it does not really give any information on the degree of cannabis exposure. As reported in the literature, there is a dose-response relationship between cannabis consumption and risk of psychotic disorder [2]. Frequency is one of the parameters of cannabis consumption that can modulate the risk for psychosis [26]. In the Palermo sample, cases who smoked cannabis were four time more likely to be frequent users than controls, who tended to use cannabis in more a sporadic way. Furthermore, in line with the GAP study findings [3], cases were 7.5 times more likely to smoke cannabis everyday compared to controls. While these results confirm the role of frequency of cannabis use in increasing the risk of developing psychotic disorder, they prevent any firm conclusions about direction of causality. However, a meta-analysis of prospective studies demonstrated that the effect of cannabis use on psychosis was not fully accounted by prodromal psychotic symptoms that may had driven cannabis use, and did not simply reflect the acute psychotogenic effect of cannabis [10]. Arsenault et al. reported an association between earlier age at first cannabis use and a higher risk of schizophrenia [9]. In Palermo sample, cases started smoking cannabis significantly earlier than controls; in fact, cases were more likely than healthy controls to have started cannabis consumption before the age of 15 years. This is interesting because some authors suggested that cannabis consumption may impact on brain development, and that early adolescence may, therefore, be a critical period for effects that do not occur when exposure begins later [27].

These results confirm the different pattern of cannabis consumption in people affected by psychosis and this may lead to consider cannabis as a contributing factor in the aetiology of psychotic disorders.

We controlled for the role of possible confounders as socio-demographic (age, gender, level of education and employment) and other environmental risk factors (other drug use and stimulant use). Demonstrating that frequency of use and early cannabis consumption is associated to an increased risk of psychosis may have relevance in public health prevention strategies and in organizing specific educational programs for adolescents.

This study has some limitations. Only one third of the FEP cases identified in the incidence part of the study were recruited in the case control analyses, but reassuringly there were not significant differences in terms of gender, ethnicity migration, level of education between participants and non-participants. For the selection of controls, an effort has been made to get a representative sample of the general population and controls were similar on a number of socio-demographic factors (age, gender, migrant status, level of education) to the population the cases come from. We do not think that selection bias might have influenced the results. A further source of bias is recall bias, because the information on the exposure was collected after the disease onset. However, it is unlikely that cannabis consumption was under-reported in our sample; in fact, lifetime cannabis consumption – both in cases (44%) and controls (56.7%) – was higher than in the Italian general population (22%). Furthermore, previous studies explored the impact of cannabis potency on psychosis risk [3], in our sample however, we did not have the chance to measure the effect of low and high potency kinds of cannabis due to the low exposure in Palermo to high potency cannabis (only 3 cases and 4 controls had ever tried high potency cannabis).

Conclusions

In the present study patients were more likely than healthy controls to have started to smoke cannabis before 15 years, and to have a higher frequency of use. Our data support an association between cannabis exposure and especially of everyday cannabis consumption and the risk of psychosis; however we are aware that the retrospective study design does not allow drawing definite conclusions about direction of causality.

Take home messages for psychiatric care

- Frequent cannabis use may increase the risk of developing psychosis
- Smoking cannabis in early adolescence may lead to psychosis

References

1 Henquet C, Murray RM, Linszen D, et al. *The environment and schizophrenia: the role of cannabis use.* Schizophr Bull 2005;31:608-12.

2 Moore THM, Zammit S, Lingford-Hughes A, et al. *Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review.* Lancet 2007;370:319-28.

3 Di Forti M, Morgan C, Dazzan P, et al. *High-potency cannabis and the risk of psychosis*. Br J Psychiatry 2009;195:488-91.

4 Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. *Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology.* Neuropsychopharmacology 2010;35:764-74.

5 Thornicroft G. *Cannabis and psychosis. Is there epidemiological evidence for an association?* Br J Psychiatry 1990;157:25-33.

6 Mathers DC, Ghodse AH. *Cannabis and psychotic illness*. Br J Psychiatry 1992;161:648-53.

7 D'Souza DC, Perry E, MacDougall L, et al. *The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis*. Neuropsychopharmacology 2004;29:1558-72.

8 Andréasson S, Allebeck P, Engström A, et al. *Cannabis and schizophrenia. A longitudinal study of Swedish conscripts*. Lancet 1987;2:1483-6.

9 Arseneault L, Cannon M, Poulton R, et al. *Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study.* BMJ 2002;325:1212-3.

10 Arseneault L, Cannon M, Witton J, et al. *Causal association between cannabis and psychosis: examination of the evidence*. Br J Psychiatry 2004;184:110-7.

11 Zammit S, Allebeck P, Andreasson S, et al. *Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study.* BMJ 2002;23:325:1199.

12 van Os J, Bak M, Hanssen M, et al. *Cannabis use and psychosis: a longitudinal population-based study.* Am J Epidemiology 2002;156:319-27.

13 Fergusson DM, Horwood LJ, Swain-Campbell NR. *Cannabis dependence and psychotic symptoms in young people*. Psychol Med 2002;33:15-21.

14 Large M, Sharma S, Compton MT, et al. *Cannabis use and earlier onset of psychosis: a systematic meta-analysis*. Arch Gen Psych 2011;68:555-61.

15 Donoghue K, Doody GA, Murray RM, et al. *Cannabis use, gender and age of onset of schizophrenia: data from the ÆSOP study.* PsychiatryRes 2014;215:528-32.

16 Caspi A, Moffitt TE, Cannon M, et al. *Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction.* Biol Psychiatry 2005;57:1117-27.

[17] Henquet C, Rosa A, Krabbenddam L, et al. *An experimental study of catechol-o- methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition*. Neuropsychopharmacology 2006;31:2748-57.

[18] Thiselton DL, Vladimirov VI, Kuo PH, et al. *AKT1 is associated with schizophrenia across multiple symptom dimensions in the Irish study of high density schizophrenia families.* Biol Psychiatry 2008;63:449-57.

[19] Bolog Z, Kiss I, Bolcs KM. *New schizophrenia loci may converge on the same cellular mechanism: the AKT pathway.* Am J Psychiatry 2012;169:335.

[20] van Winkel R, van Beveren NJ, Simons C, et al. *AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder*. Neuropsychopharmacol 2011;36:2529-37.

[21] Di Forti M, Iyegbe C, Sallis S, et al. *Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users*. Biol Psychiatry 2012;72:811-6.

[22] World Health Organization. *Schedules for Clinical Assessment in Neuropsychiatry (SCAN)*. Geneva: 1992.

[23] Mallett R, Leff J, Bhugra D, et al. *Social environment, ethnicity and schizophrenia. A case-control study.* Soc Psychiatry Psychiatr Epidemiol 2002;37:329-35.

[24] Bebbington P, Nayani T. *The Psychosis Screening Questionnaire*. Int J Methods Psychiatr Res 1995;5:11-9.

[25] Casadio P, Fernandes C, Murray RM, et al. *Cannabis use in young people: the risk for schizophrenia.* Neurosci Biobehav Rev 2011;35:1779-87.

[26] Di Forti M, Sallis H, Allegri F, et al. *Daily use, especially of high-potency cannabis drives the earlier onset of psychosis in cannabis users.* Schizophr Bull 2013;40:1509-17.

[27] Wilson W, Mathew R, Turkington T, et al. *Brain morphological changes and early marijuana use. A magnetic resonance and positron emission tomography study*. J Addict Dis 2010;19:1,1-22.

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BIPOLAR DISORDER AND SUBTHRESHOLD SYMPTOMS OF BORDERLINE PERSONALITY DISORDER: IMPACT ON QUALITY OF LIFE

Abstract

Objectives: The nature of the relationship between bipolar disorder (BD) and borderline personality disorder (BPD) has been a field of debate in the last two decades. Literature's data show that as many as 20 % of patients with BPD meet criteria for bipolar I disorder. Furthermore, the presence of BPD has a high impact in the course of BD in terms of prognosis and scores of global functioning. However, a large number of BD patients shows BPD subthreshold symptoms and little is known about their impact in the course of BD. The purpose of the study is to evaluate the impact of BPD subthreshold symptoms in patients with a primary diagnosis of BD in terms of patient's prognosis and quality of life.

Materials and methods: The sample consisted of 29 outpatients (15 males and 14 females), aged between 24 and 66 years old suffering from BD seeking treatment at the Psychiatry Department of Siena Hospital. BD diagnosis was determined following the diagnostic criteria of the DSM IV TR. Patients were assessed with SCID II (Structured Clinical Interview for DSM IV axis II Disorders) and Q-LES (Quality of life enjoyment and satisfaction questionnaire). SCID II was administrated to assess the diagnosis of BPD (5 positive item) or the presence of BPD subthreshold symptoms (3-4 positive item). Additional clinical and prognostical data were also evaluated: age of disorder's onset, working and social condition, self-injury behaviours and suicide attempts, substance abuse, pharmacotherapy's degree of adherence. Patient's sample was divided in three groups with regard to BD diagnosis and SCID II assestment: BD (n = 11), BD and subthreshols symptoms of BPD (n = 8), BD and BPD (n = 10). A medium percentage of QLES-Q scores and of values of the other clinical data was calculated for every group.

Results and conclusions: Patients with DB and BPD showed an earlier age of symptom's onset than patients with a single diagnosis of BD. Moreover, subjects with BD and BPD subthreshold symptoms showed an intermediate age of onset compared with the other subgroups. Overall score results of Q-LES-Q are lower in the BD and subthreshold symptoms of BPD group with the only exception for the social relationships area where lower scores were founded in the group of BD+BPD patients (according to the specific relational instability of patients with BPD). The higher level of relational functioning was found in the BD group since these patients have more likely periods without symptoms of the disease than the other groups. The higher percentage values of abuse and self-injury behaviors was found in the BD+BPD group, confirming the natural history of BPD. With regard to psychopharmacological therapy, besides the use of mood stabilizers due to the comorbidity with BD, results showed a more widespread use of atypical antipsychotics in the BD+SBPD group. This results may be explained with the greater degree of adherence of this group of patients. The limit of the study is the small sample size. Larger controlled, prospective trials are warranted to confirm our preliminary results.

Key words: borderline personality disorder, quality of life enjoyment and satisfaction questionnaire, pharmacotherapy

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Introduction

The nature of the relationship between bipolar disorder (BD) and borderline personality disorder (BPD) has been a field of debate in the last two decades [1].
Literature's data show that as many as 20% of patients with BPD meet criteria for bipolar I disorder [2].
BD can be mistaken for symptoms of BPD masking Axis I disorder [3].
The high prevalence of residual symptoms in patients affected by BD and its unstable course makes difficult to distinguish the two pathological conditions.
However, a large number of BD patients shows BPD subthreshold symptoms (BPDS) and little is know about their impact in the course of BD.
There are several studies that show the use of drug therapy on affective dysregulation symptoms of patients with BPD [4].
Literature's data show that, the presence of BPD has a high impact in BD' s prognosis and scores of global functioning.
Furthermore, some studies show how the comorbidity of BPD affects the severity and the number of hospitalizations of BD and may anticipate episode onset.
Actually no specific pharmacological treatment is approved for BPD.
However, there is evidence that some core symptoms of Borderline Personality Disorder can be successfully treated with antipsychotics and mood stabilizers [5].
The purpose of the study is to evaluate the impact of BPD subthreshold symptoms in patients with a primary diagnosis of BD in terms of patient's prognosis and quality of life.

Materials and methods

The sample consisted of 29 outpatients (15 males and 14 females), aged between 24 and 66 years old suffering from BD seeking treatment at the Psychiatry Department of Siena Hospital.
BD diagnosis was determined following the diagnostic criteria of the DSM IV TR.
Patients were assessed with SCID II (Structured Clinical Interview for DSM IV axis II Disorders) and Q-LES-Q (Quality of life enjoyment and satisfaction questionnaire).
Q-les-Q t is a self-assessment scale developed in order to easily obtain a sensitive measure of the degree of pleasure and satisfaction that subjects with both psychological and somatic disease, experience in the different areas which make up daily life (Endicott et al., 1993).
Q-LES-Q consists of 58 items that explore five different areas: physical health (13 items), subjective feelings (14 items), social relationships (11 items), leisure activities (6 items), employment (14 items).
SCID-II interview was administrated to assess the diagnosis of BPD (5 positive item) or the presence of BPD subthreshold symptoms (3-4 positive item).
Additional clinical and prognostical data were also evaluated: age of disorder's onset, working and social condition, self-injury behaviours and suicide attempts, substance abuse, pharmacotherapy's degree of adherence.
Patient's sample was divided in three groups with regard to BD diagnosis and SCID II assessment BD (n = 11), BD and subthreshols symptoms of BPD (n = 8), BD and BPD (n = 10).
A medium percentage of QLES-Q scores and of values of the other clinical data was calculated for every group.

Results and conclusions

Conclusions are conditioned by the small sample size.
Patients with DB and BPD showed an earlier age of symptom's onset than patients with a single diagnosis of BD. Moreover, subjects with BD and BPD subthreshold symptoms showed an intermediate age of onset compared with the other subgroups.
Overall score results of Q-LES-Q are lower in the BD and subthreshold symptoms of BPD group with the only exception for the social relationships area where lower scores were founded in the group of BD+BPD patients (according to the specific relational instability of patients with BPD).
The higher level of relational functioning was found in the BD group since these patients have more likely periods without symptoms of the disease than the other groups.
The higher percentage values of abuse and self-injury behaviors was found in the BD+BPD group, confirming the natural history of BPD.
With regard to psychopharmacological therapy, besides the use of mood stabilizers due to the comorbidity with BD, results showed a more widespread use of atypical antipsychotics in the BD+BPD subthreshold symptoms group.
This results may be explained with the greater degree of adherence of this group of patients.
The limit of the study is the small sample size. Larger controlled, prospective trials are warranted to confirm our preliminary results.

Table I. Comparison between the three study subgroups.

Diagnosis Number of patients	BD 38% (n = 11/29)	BD+BPD subthreshold 28% (n = 8/29)	BD+BPD 34% (n = 10/29)
Age at first contact with specialist	37 years	30 years	28 years
TS and self-harm	0%	12% (n = 1/8)	33% (n = 3/10)
Behaviour of alcohol abuse or psychoactive substances	18% (n = 2/11)	50% (n = 4/8)	50% (n = 5/10)
Marital status conjugate	72% (n = 8/11)	37 % (n = 3/8)	30% (n = 3/10)
Q-les-Q general (median of scores)	55%	45%	53%
Q-les-Q physical health	69%	62%	65%
Q-les-Q emotions	58%	48%	60%
Q-les-Q social relations	65%	55%	52%
Drug theraphy with antideprassants	55% (n = 6/11)	75% (n = 6/8)	70% (n = 7/10)
Drug theraphy with mood stabilizers	91% (n = 10/11)	87% (n = 7/8)	90% (n = 9/10)
Drug theraphy with antipsychotics	55% (n = 6/11)	75% (n = 6/8)	50% (n = 5/10)

Take home messages for psychiatric care

- There is evidence that some core symptoms of Borderline Personality Disorder can be successfully treated with antipsychotics and mood stabilizers
- The use of mood stabilizers due to the comorbidity with BD, results showed a more widespread use of atypical antipsychotics in the BD+BPD subthreshold symptoms group
- Score results of Q-LES-Q are lower in the BD and subthreshold symptoms of BPD group with the only exception for the social relationships area where lower scores were founded in the group of BD+BPD patients

Future target will expand the sample, analyze other variables such as the number of episodes and the remission time.

References

1 Borda JP. *Self over time: another difference between borderline personality disorder and bipolar disorder.* J Eval Clin Pract 2016 May 3. doi: 10.1111/jep.12550. [Epub ahead of print]

2 Comtois KA, Cowley DS, Dunner DL, et al. *Relationship between borderline personality disorder and Axis I diagnosis in severity of depression and anxiety.* J Clin Psychiatry 1999;60:752-8.

3 Gross R, Olfson M, Gameroff M, et al. *Borderline personality disorder in primary care*. Arch Intern Med 2002;162:53-60.

4 Bellino S, Paradiso E, Boggetto F. *Efficacy and tolerability of pharmacotherapies for borderline personality disorder.* CNS Drugs 2008;22:671-92.

5 Lieb K, Vollm B, Rucker G, et al. *Pharmacotheraphy for borderline personality disorder: cochrane systematic review of randomised trials.* Br J Psychiatry 2010;196.

AGITATION AND AGGRESSION IN THE ELDERLY: PHARMACOLOGICAL STRATEGIES IN A COURT OF 84 TUSCANY PHYSICIANS

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Abstract
Agitation and aggression in elderly people is a common issue and physicians may have to deal with this condition during their medical practice. It may be due to several causes such as mental disorders or medical conditions. We decided to submit a questionnaire to 47 psychiatrists and 37 internists, in order to record which pharmacological treatment and method of administration they usually employ and the reason of their choice. The drug mostly used in the treatment of agitation and aggression, regardless of the etiology, was Promazine followed by Chlorpromazine. These drugs were primarily administrated by injection, with slightly differences depending on the causes of agitation and aggression. The choice of the drug appeared to be mostly moved by its safety profile. Second generation antipsychotics were barely preferred, in spite of current guidelines suggest

Key words: agitation, aggression, elderly, antipsychotics

Introduction

Agitation is an extreme form of arousal that is associated with increased verbal and motor activity. These symptoms are caused by a variety of etiologies, such as mental disorders, dementia, delirium or other medical conditions [1]. Agitation and aggression in elderly people is a common issue that physicians may have to deal with during their medical practice. In spite of its frequency there isn't an univocal treatment and management among physicians [2]. It's reported that in up to 25% of cases, only the symptoms of agitation are treated, without acting on its causes [3]. This article aims to record which pharmacological treatment and route of administration a court of psychiatrists and internists usually employ in management of agitation and the reason for their choice.

Materials and method

We created a questionnaire and we sent it to 60 psychiatrists and 60 internal medicine physicians working in Tuscany in which they were asked to indicate which pharmacological treatment and route of administration they usually employ among 32 medications commonly used in the treatment of agitation and aggression in a scale from 1 to 4 (in which 1 meant "never", 2 "sometimes", 3 "often" and 4 meant "always"). 47 psychiatrists and 37 internal medicine physicians actually applied to the questionnaire. The questionnaire was made of 5 sections, the first one regarding

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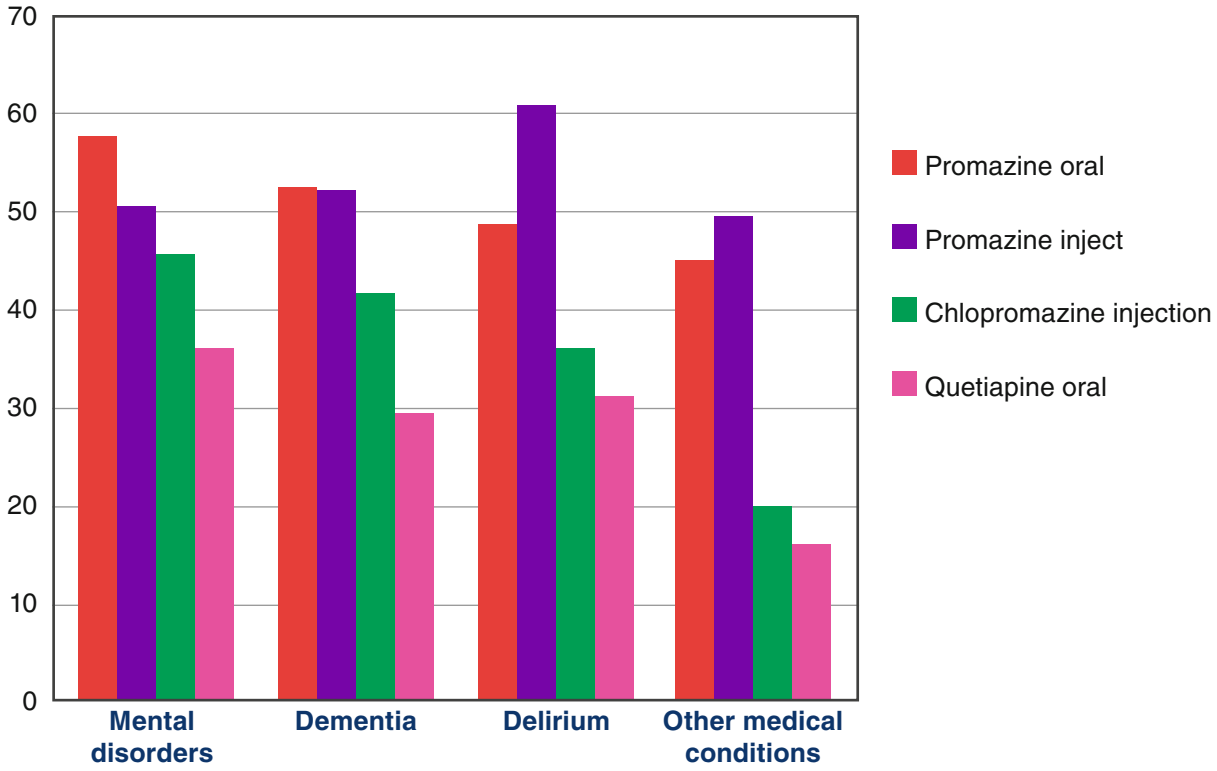

FIGURE 1.
Most used drugs in agitation and aggression.

the treatment of agitation due to mental disorders, the second due to delirium, the third due to dementia and the fourth due to other medical conditions. In the fifth section physicians were asked to indicate in a scale from 1 to 5 (in which 1 meant "not at all", 2 "little", 3 "enough", 4 "much" and 5 meant "very much") the reasons for their choice (experience, prompt action, safety, availability, previous treatments). We made a statistical analysis of the utilization of drugs that reached 50% of the sample, considering the total percentage of "often-always" answers. We applied the CHI-square test in order to evaluate if the difference in drug prescription between psychiatrists and internal medicine physicians was statistically relevant.

Results

Promazine (oral or via injection) was the most frequently administered drug in patients with agitation due to psychiatric disorders, with a slight preference for the oral route of administration (57.8% *vs* 50.6%). Moreover, chlorpromazine administered via injection was chosen by the 45,8% of physicians.
In case of delirium, the 60.7% of physicians preferred promazine via injection, while for dementia both the oral and the intravenous/intramuscular formulations received more preferences (52,4% and 52,3% respectively). In addition, promazine was preferred for agitation associated with organic diseases (Fig. 1).
When asked about importance of the experience with the drug in choosing it, 53% of the sample answered "much". Similar results were reported for the early onset of action (57,8%), safety (59%) and previous treatment efficacy (55,4%). When asked about importance of prompt availability of the drug in choosing it, only 40,2% answered "much".
There was a statistical difference in clinical practice between specialists in Psychiatry and other field physicians, mostly regarding the use of second generation antipsychotic medications (Tab. I). Statistical difference between psychiatrist and other physicians was found in the use of oral Promazine in patients with agitation due to dementia (66,7% *vs* 35,1%, p = 0,004) and other medical conditions (55,3% *vs* 31,4%, p = 0,032) and in the use of oral Olanzapine in agitation due to other medical conditions (15,6% *vs* 0%, p = 0,015)

Conclusions

The drug mostly used in the treatment of agitation and aggression, regardless of the reason for use, was Promazine followed by Chlorpromazine. These drugs

Table I. Difference in clinical practice between psychiatrists and internists.

	Mental disorder	Dementia	Delirium	Other medical condition
Promazine oral	61.7% (P) 52.8% (O)	66.7% (P) 35.1% (O)	51.1% (P) 45.9% (O)	55.3% (P) 31.4% (O)
Promazine injection	51.1% (P) 50% (O)	48.9% (P) 56.8 (O)	59.6% (P) 62.2% (O)	51.1% (P) 45.7% (O)
Chlorpromazin e oral	51.1% (P) 38.9% (O)	31.9% (P) 54.1% (O)	29.8% (P) 43.2% (O)	13.3% (P) 28.6% (O)
Haloperidol oral	40.4% (P) 38.9% (O)	19.1% (P) 29.7% (O)	29.8% (P) 27.8% (O)	13% (P) 20% (O)
Zuclopenthixol oral	25.5% (P) 33.3 (O)	21.3% (P) 32.4% (O)	25.5% (P) 40.5% (O)	13% (P) 22.9% (O)
Quetiapine oral	46.8% (P) 22.2% (O)	35.6% (P) 22.2% (O)	36.2% (P) 25% (O)	19.1% (P) 11.4% (O)
Olanzapine oral	25.5% (P) 0% (O)	14.9% (P) 10.8% (O)	17% (P) 10.8% (O)	15.6% (P) 0% (O)

P: Psychiatrist; O: Physicians other than Psychiatrist
** difference statistically significant*

were primarily administrated by injection, with slight differences depending on the causes of agitation and aggression. The choice of the drug appeared to be mostly due to its perceived efficacy and safety profile. Second generation antipsychotics were not used as frequently as the current guidelines suggest [4]. These results actually follow the international trend, showing that in emergency department second generation antipsychotics are rarely used, mostly in oral administration and in association with benzodiazepines [5]. This is also due to low availability of second generation antipsychotics in emergency departments and insufficient training among medical specialists other than psychiatrists. It would be crucial to standardize managing and treatment of agitation and aggression according to current guidelines, among hospitals and emergency departments. In order to achieve this goal it may be useful organize retraining courses, intended to sensitize health workers to the new available drugs.

Take home messages for psychiatric care

- If possible, choose SGA and oral

References

1 Nordstrom K, Zun LS, Wilson MP, et al. *Medical evaluation and triage of the agitated patient: Consensus Statement of the American Association for Emergency Psychiatry Project BETA Medical Evaluation Workgroup*. West J Emerg Med 2012;13:3-10.

2 Holloman GH, Zeller SL. *Overview of project BETA: best practices in evaluation and treatment of agitation*. West J Emerg Med 2012;13:1-2.

3 Yudofsky SC, Kopecky HJ, Kunik M, et al. *The overt agitation severity scale for the objective rating of agitation*. J Neuropsych Clin Neurosc 1997;9:541-8

4 Garriga M, Pacchiarotti I, Fagiolini A, et al. *Assessment and management of agitation in psychiatry: expert consensus.* E World J Biol Psychiatry 2016;17:86-128.

5 Wilson MP, Minassian A, Bahramzi M, et al. *Despite expert raccomandations, second-generation antipsychotics are not often prescribed in the emergency department.* J Emerg Med 2014;46:808-13.

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PSYCHIATRIC SYMPTOMS PRECEDING ADDICTIVE DISORDERS

Abstract

Brief introduction. Aim of this study was to investigate a possible temporal and causal connection between psychiatric disorders and addictive behaviour with the goal to prepare the ground for studies on the best prevention strategies.

Materials and methods. We evaluated a sample of 105 patients with a diagnosis of addiction disorder, treated in mental health care centers in Siena. Patients included had to be 18 years old, have good mastery of Italian language, be able to give informed consent and free of significant cognitive deficits. Each patient was administered a demographic form followed by a SCID I (Structured Clinical Interview for DSM-IV Axis I Disorders) and a SCID II (Structured Clinical Interview for DSM-IV Axis II Disorders) both extended with a section containing information about the age of onset of each item.

Results. Over 90% of the sample had comorbidity on Axis I or Axis II, with a clear majority of mood and anxiety disorders (Axis I, DSM IV) and of Cluster B disorders (Axis II DSM V) respectively. The age of onset of mood disorders was, on average, 3 to 6 years before the outbreak of drug abuse in more than 20% of the sample, whereas more than 50% of our sample endorsed an anxiety disorder that preceded the onset of drug addiction. Comorbidity with Axis II disorders was highly represented (Tab. I): 85% of the sample presented a personality disorder and over 50% had multiple diagnosis. All subjects with a diagnosis of personality disorder showed the first symptoms approximately 2 years before the beginning of the addictive behaviour.

Conclusions. This study suggests that addiction diseases are very often preceded by other psychiatric disorders and that preventive actions are possible during the time window between early psychiatric symptoms and the first contact with substances of abuse. In particular, early detection and efficient treatment of the psychiatric disorder most strongly associated with drug abuse might prevent the outbreak of a full-blown substance-related disorder. Prospective studies are necessary to confirm the direction of causality and evaluate if the two phenomena are directly correlated with a cause-effect relationship.

Key words: addiction disorder, comorbidity, anxiety disorders, cluster B

Introduction

The term “Dual Diagnosis” describes the simultaneous presence, in the same patient, of a mental and an addictive disorder [1].

Several studies show how psychiatric symptoms could be responsible for the start of drug abuse, often with the aim of self-medication [2-5]. It’s possible to assume that an early detection of psychiatric symptoms or personality characteristics (even without a full-blown diagnosis) could be a target for prevenction strategies to mitigate risk and avert substance-related problems later in life [6].

Aim of this study was to investigate a possible temporal and causal connection between psychiatric disorders and addictive behaviour with the goal to prepare the ground for studies on the best prevention strategies.

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Materials and methods

We evaluated a sample of 105 patients with a diagnosis of addiction disorder, treated in mental health care centers in Siena. Interviewers described the project to participants and informed them that they should have received no compensation. Patients included had to be 18 years old, have good mastery of Italian language, be able to give informed consent and free of significant cognitive deficits. Each patient was administered a demographic form with informations about the age of access to mental health care center, family history of mental disorders, past therapy and actual therapy and present history of drug abuse. Demographic form was followed by a SCID I (Structured Clinical Interview for DSM-IV Axis I Disorders) and a SCID II (Structured Clinical Interview for DSM-IV Axis II Disorders) both extended with a section containing information about the age of onset of each item. Finally our data were incorporated into a database by a software (Excel 2007) and statistically elaborated by SPSS Statistic Base, version 10.

Results

Our results are summarized in Table I. Over 90% of the sample had comorbidity on Axis I or Axis II, with a clear majority of mood and anxiety disorders (Axis I, DSM IV) and of Cluster B disorders (Axis II, DSM IV) respectively. In particular, the age of onset of Mood Disorders was, on average, 3 to 6 years before the outbreak of drug abuse in more than 20% of the sample, with a predominance of Mayor Depression. More than 50% of our sample endorsed an Anxiety Disorder that preceded the onset of drug addiction, with peaks as high as 25% concerning Social Phobia (with an outbreak of 9 years before drug abuse) and as high as 20% of the sample concerning Generalized Anxiety Disorder (with on outbreak of 7 years before drug abuse). In 40% of the patients with a diagnosis of Post-Traumatic Stress Disorder (PTSD) the onset of psychiatric symptoms predates the addictive behavior by more than 8 years (mean): the latter result seems to clearly confirm how traumatic events could lead to addictive behavior, especially when a self-medication mechanism is involved. Explosive Intermittent Disorder was present in 31.4% of the sample and, among these, the 44% presented mental disorder before drug abuse.

Comorbidity with Axis II disorders was highly represented: 85% of the sample presented a personality disorder and over 50% had multiple diagnosis. All subjects with a diagnosis of personality disorder showed the first symptoms approximately 2 years before the beginning of the addictive behavior, with the exception of Adult Antisocial Personality Disorder which, because of its criteria, is diagnosed after the age of 15.
The most represented Axis II Disorder in our sample was Borderline Personality Disorder with a percentage of 36,2% of subjects; again, the age of onset of psychiatric symptoms preceded drug abuse with the mean time of 7 months.
The presence of this time window shows how an early detection and treatment of psychiatric symptoms could be essential in the prevention of the occurrence of an Addictive Disorder.

Conclusions

The aim of our study was to detect, retrospectively, the presence of psychiatric risk factors in our sample of 105 patients with addictive disorder, in order to understand how they could be responsible for addictive behaviour. During adolescence mental disorders are risks factors as frequent as unnoticed or hard to detect, while it should early act upon them in order to avoid self-medication mechanisms and so the outbreak of an addiction [7].
Our results seems to confirm that it could be present a causality reletionship between psychiatric disorders and drug abuse. In fact over 90% of the sample had comorbidity on Axis I or Axis II, with a clear majority of mood and anxiety disorders (Axis I, DSM IV) and of Cluster B disorders (Axis II DSM IV) respectively. Comorbidity with Axis II disorders was highly represented: 85% of the sample presented a personality disorder and over 50% had multiple diagnosis.
This study suggests that addiction diseases are very often preceded by other psychiatric disorders and that preventive actions are possible during the time window between early psychiatric symptoms and the first contact with substances of abuse. In particular, early detection and efficient treatment of the psychiatric disorder most strongly associated with drug abuse might prevent the outbreak of a full-blown substance-related disorder. Prospective studies are necessary to confirm the direction of causality and evaluate if the two phenomena are directly correlated with a cause-effect relationship.

Table I. Results.

	Frequency (total)	Frequency (previous diagnosis)	Years beetween diagnosis (Mean)	St. Deviation
Axis I	Mayor depression	59 (56.2%)	14	-6,00 (-29;-1)
	Bipolar I	22 (21.0%)	5	-3.45 (-4;-2)
	Bipolar II	7 (6.7%)	3	-2.30 (-3;-1)
	Panic disorder with agoraphobia	23 (21,9%)	6	-5.83 (-11;-1)
	Panic disorder without agoraphobia	8 (7.6%)	2	-9.00 (-15;-3)
	Social phobia	29 (27.6%)	27	-8.96 (-36;-2)
	GAD	35 (33.3%)	21	-6.90 (-33;-1)
	OCD	8 (7.6%)	2	-7.00 (-12;-2)
	Specific phobia	18 (17,1%)	17	-6.76 (-24;-2)
	PTSD	13 (12.4%)	5	-8.40 (-14;-1)
	Schizophrenia	3 (2.9%)	0	/
	Schizoaffective	5 (4.8%)	1	-4.00
	Delusional disorder	4 (3.8%)	2	-7.00 (-11;-3)
	Brief psychotic disorder	3 (2.9%)	0	/
	Nervous anorexia	10 (9.5%)	3	-4.67 (-12;-1)
	Nervous bulimia	6 (5.7%)	0	/
	Intermittent explosive disorder	33 (31.4%)	15	-3.73 (-9;-1)
Axis II	Avoidant P.D.	17 (16.2%)	/*	-3.41
	Dependent P.D.	8 (7.6%)	/*	-1.75
	Obsessive-compulsive P.D.	21 (20%)	/*	-2.10
	Passive-aggressive P.D.	15 (14,3%)	/*	-0.67
	Depressive P.D.	12 (11.4%)	/*	-2.33
	Paranoid P.D.	15 (14.3%)	/*	-0.67
	Schizoid P.D.	9 (8.6%)	/*	-0.89
	Histrionic P.D.	2 (1.9%)	/*	-0.50
	Narcissistic P.D.	5 (4.8%)	/*	-2.60
	Borderine P.D.	50 (47.6%)	/*	-0.66
	Adult Antisocial P.D.	38 (36.2%)	/*	2.22

** The age of onset of Axis II disorders is precocious and usually precedes toxicomanic behaviour, with the exception of Adult Antisocial P. D. which, by criteria, it's diagnosed later in life.*

Take home messages for psychiatric care

- Aim of this study was to investigate a possible temporal and causal connection between psychiatric disorders and addictive behaviour with the goal to prepare the ground for studies on the best prevention strategies
- Our results seems to confirm that it could be present a causality reletionship between psychiatric disorders and drug abuse
- Prospective studies are necessary to confirm the direction of causality and evaluate if the two phenomena are directly correlated with a cause-effect relationship

References

1 Rigliano, P. *Doppia diagnosi. Tra tossicodipendenza e psicopatologia*. Milano: Cortina Raffaello 2004.

2 Toumbourou JW, Stockwell T, Neighbors C, et al. *Interventions to reduce harm associated with adolescent substance use.* Lancet 2007;369:1391-401.

3 Winters KC, Fawkes T, Fahnhorst T, et al. *A synthesis of exemplary drug abuse prevention programs in the United States.* J Subst Abuse Treat 2007;32:371-80.

4 Hawkins D, Catalano R, Miller J. *Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: Implications for substance abuse prevention*. Psychol Bull 1992;112:64-105.

5 Cuijpers P. *Three decades of drug prevention research*. Drugs: Educ Prev Policy 2009:7-20.

6 Moss HB, Chen CM, Yi HY. *Early adolescent patterns of alcohol, cigarettes, and marijuana polysubstance use and young adult substance use outcomes in a nationally representative sample.* Drug Alcohol Depend 2014;136:51-62.

7 Cassano GB, Tundo A. *Psicopatologia e clinica psichiatrica.* Torino: UTET 2008.