## PSYCHOMOTOR AGITATION IN PSYCHIATRY: AN ITALIAN EXPERT CONSENSUS

**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<sup>1</sup>. 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"<sup>1</sup>. Citrome<sup>2</sup> described the hallmark of PMA as excessive motor or verbal activity. Battaglia<sup>3</sup> 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 <sup>56</sup>. 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<sup>7</sup>. 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"<sup>8</sup>. Irrespective of its definition, from a phenomenological point of view PMA is best considered as a transnosological syndrome<sup>9</sup>, 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 <sup>5 10</sup>. If not adequately treated, PMA can rapidly escalate up to the highest levels of severity <sup>11-13</sup>, with potentially dangerous behaviors and a high risk

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Emilio Sacchetti emilio.sacchetti@unibs.it of personal injuries – for the patient, for accompanying people, for the staff – and property damage <sup>3 5</sup>. 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 <sup>14</sup>.

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<sup>7</sup> can be divided into the following main categories: internistic, surgical or neurological conditions, psy-chiatric disorders, and substance intoxications/with-drawals (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
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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<sup>15</sup> and/or substance abuse<sup>16 17</sup> 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<sup>18</sup>. 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 <sup>19</sup> 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)<sup>20</sup>.

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 <sup>21</sup>. 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 <sup>22</sup>. Furthermore, approximately 70% and 65% of these episodes, in schizophrenia and bipolar disorder respectively, have been classified as mild to moderate <sup>22</sup>.

Prevalence rates of PMA ranging from 4.3% 23 to 10% <sup>19 24-26</sup> 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 <sup>28</sup>. Considering that PMA is reported to be a "common symptom" in patients with schizophrenia, bipolar disorder or dementia who seek psychiatric emergency services <sup>28-30</sup>, about 1.7 million visits per year in the United States are likely to involve patients potentially at risk for agitation <sup>19</sup>. 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 <sup>31</sup>. 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<sup>32</sup>.

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

and 29% <sup>38</sup> were reported in cases of bipolar disorder I. Serretti et al. <sup>39</sup> reported a prevalence of PMA of 87.9% in bipolar disorder I and 52.4% in bipolar disorder II. According to Goodwin and Jamison <sup>40 41</sup>, 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 <sup>42</sup>. Contrary to previous observations <sup>43</sup>, these data suggest that PMA could be related to bipolarity in major depression <sup>42</sup>.

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%<sup>44</sup>. 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<sup>45</sup>. 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<sup>46</sup>.

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<sup>6</sup>, 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<sup>48</sup>. 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 <sup>50</sup>. 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 <sup>51</sup>. 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 <sup>24</sup>. 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<sup>54</sup>. In Italy, in a 7-year study of 3507 admissions to a psychiatric ward, the cumulative incidence of aggression was 11.6% per admission <sup>55</sup>. 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 <sup>56</sup>.

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<sup>59</sup>, the prevalence of violent episodes was 20% in the period preceding first hospitalization <sup>60 61</sup>, 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% <sup>65</sup> to 64% <sup>66</sup>.

# 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.<sup>67</sup> 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<sup>73</sup>.

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 ( $\in$  71 vs  $\in$  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.<sup>20</sup>, 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<sup>20</sup>.

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<sup>7</sup>.

When a person arrives with PMA, triage, initial assessment and de-escalation should occur at the same time <sup>10</sup>, 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% <sup>75</sup>.

Anamnestic data or the presence of certain signs or symptoms can direct the diagnosis toward a specific underlying medical illness <sup>7</sup>. 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 776. 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<sup>7</sup>; 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 <sup>79 80</sup>. 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<sup>81</sup>. 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 <sup>7</sup>. In hypoxia, key signs include abnormal breathing patterns, dyspnea or tachypnea, and impaired oxygen saturation<sup>7</sup>. 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 <sup>83</sup>. When a person ingests toxic levels of psychotropic drugs, disorientation, somnolence or agitation may be present<sup>7</sup>. 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 <sup>84</sup>, whereas in serotonin syndrome myoclonus and hyperreflexia occur <sup>85</sup>.

Alcohol and/or substance intoxication and withdrawal syndromes are common causes of PMA <sup>86</sup>. 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 <sup>7</sup>. The patient may have disorientation, hallucinations, seizures, and autonomic instability <sup>86</sup>.

If no medical cause is found for PMA, the patient can be seen by psychiatrists <sup>7</sup>.

#### 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 <sup>10</sup>. 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 <sup>10</sup>. 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<sup>10</sup>. 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<sup>87</sup> 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 <sup>10</sup>. 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 <sup>8</sup>. 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 <sup>10</sup>. If there is no psychosis but symptoms of mania are present, the treatment is the same as for the patient with psychosis <sup>88</sup>. In PMA due to nonpsychotic depression or an anxiety disorder, the underlying anxiety should be treated <sup>89</sup>; 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 <sup>90</sup>.

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 <sup>10</sup>. 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 <sup>10</sup>.

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<sup>10</sup>.

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 <sup>91</sup>. 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 <sup>10</sup>.

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 <sup>10</sup>.

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 <sup>10</sup>.

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 <sup>10</sup>. The use of assessment tools such as the Mini Mental State Examination <sup>87</sup> or the Brief Mental Status Examination <sup>92</sup> 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<sup>10</sup>. 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 <sup>10</sup>. 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 <sup>10 94</sup>.

## 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.)<sup>5</sup>. 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 posttraumatic 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)<sup>5</sup>. 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 <sup>95</sup>, has also been successfully used in psychiatric patients presenting in the ED <sup>96</sup>. 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 ( $\leq$  21), mild (22-28), moderate (29-35), and severe ( $\geq$  36) <sup>97</sup>. 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 <sup>98</sup>. Each item is included in one of four categories ("factors") – physical/aggressive, physical/ non-aggressive, verbal/aggressive, and verbal/nonaggressive – 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 <sup>5 99</sup>.

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 <sup>100</sup>. 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 <sup>5 101</sup>.

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 <sup>102</sup>. 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 <sup>5</sup> <sup>103</sup>.

The Positive And Negative Syndrome Scale-Excited Component (PANSS-EC) is a subscale of the PANSS (developed and standardized by Kay et al.<sup>104</sup> in 1987 for patients with schizophrenia), which takes into account only the excitation component <sup>105</sup>. 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  $\geq$  14 with a score  $\geq$  4 on at least one item usually indicates a clinically significant PMA <sup>106-109</sup>, whereas a score  $\geq$  20 usually corresponds to severe agitation <sup>110</sup> <sup>111</sup>. The PANSS-EC has been widely used as an assessment tool in clinical studies of pharmacotherapy for agitation <sup>106-108 112 113</sup>; response to treatment is generally considered as a  $\geq$  40% decrease in score within 2 hours <sup>5</sup>. 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

#### (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)<sup>110</sup>. 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)<sup>114</sup>. 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 <sup>115</sup>. The NRS-R showed good reliability in the evaluation of patients with recent closed head injuries <sup>116</sup>.

The Overt Aggression Scale (OAS) includes 16 items in four domains: verbal aggression, physical aggres-

sion against objects, physical aggression against self, and physical aggression against other people<sup>117</sup>. 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<sup>118</sup>. 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 <sup>119-121</sup>, genetic <sup>122</sup>, and observational <sup>70</sup> studies, and an Italian version has been validated <sup>123</sup>.

The Aggressive Behavior Scale is a 4-item instrument measuring verbal and physical abuse, socially inappropriate behavior, and resisting care <sup>124</sup>. 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 <sup>5</sup>.

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 <sup>125</sup>. 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 <sup>126</sup>. The total score is interpreted as follows: 0 = small risk of violence; 1-2 = moderate risk of violence (preventive measures should be taken);  $\ge 3 =$  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  $\ge 3$  was predictive of a violent event in the next 24-hours <sup>126</sup>.

The McNiel-Binder Violence Screening Checklist (VSC) is also intended to evaluate the risk of violent behaviors in hospitalized psychiatric patients <sup>127</sup>. 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 <sup>5</sup>.

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<sup>128</sup>, it was recently updated to version 3 (HCR-20<sup>V3</sup>)<sup>129</sup>. 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 <sup>5</sup>.

The actual applicability of these instruments in reallife 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 <sup>5</sup> <sup>126</sup>.

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<sup>7</sup>.

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 <sup>5</sup> <sup>130</sup> <sup>131</sup>. In practice, experienced psychiatrists and psychiatric nurses are able to accurately predict violent behaviors without the use of specific assessment tools <sup>5</sup>, reaching an accuracy of more than 80% in newly admitted psychiatric patients <sup>132</sup>. 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, reguiring 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<sup>5</sup>, 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 <sup>133</sup>, as well as with the true spirit of Italian Law No. 180 of May 13, 1978<sup>134</sup>, 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 measures; 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<sup>135</sup>.

#### **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 <sup>135</sup>. 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 <sup>135</sup>.

The latest version of Project Beta<sup>90</sup> and the 2015 NICE guidelines on the management of violence and aggression <sup>136</sup> may also be applied to the broader case of PMA, because they describe how to carry out deescalation 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 <sup>90 136</sup>: 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 <sup>90</sup>.

#### 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 <sup>4</sup> <sup>135</sup> <sup>137</sup> <sup>138</sup>. This allows interaction and collaboration with the patient to be preserved, and the diagnostic and therapeutic path to be continued in a constructive manner <sup>5</sup> <sup>138</sup>.

#### **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 <sup>5 139 140</sup>. At present there is no gold standard medication for the treatment of all cases of PMA, but three classes of drugs are used most frequently for this condition: first-generation (or typical) antipsychotics (FGAs), secondgeneration (or atypical) antipsychotics (SGAs), and benzodiazepines<sup>1 135 138</sup>.

*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 <sup>138</sup>. 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 <sup>11 138</sup>. 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 <sup>138</sup>. 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 <sup>138</sup>. 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 <sup>138</sup>. 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<sup>141</sup>. 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 <sup>143</sup> <sup>144</sup>, current guidelines consider FGAs to be less preferred than atypical antipsychotics <sup>138</sup>. 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 <sup>138</sup>. FGAs also include loxapine, which shares several characteristics with atypical antipsychotics, including the antagonist effect on 5-HT2A recentors <sup>145</sup> An

ing the antagonist effect on 5-HT2A receptors <sup>145</sup>. An inhaled formulation of loxapine has been developed and recently approved <sup>146 147</sup>, and has been shown to be effective in the treatment of acute PMA <sup>109 148 149</sup>.

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  $\alpha$ -2 receptors) with varying degrees of potency depending on the individual drug <sup>138</sup>. 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% <sup>150-152</sup>. 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 <sup>138</sup>. 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 <sup>153</sup>. 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 <sup>138</sup>.

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 <sup>138</sup>. Benzodiazepines. Benzodiazepines, such as diazepam, lorazepam and clonazepam, act on the GABA receptor, the main inhibitory neurotransmitter in the brain <sup>138</sup>. 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 <sup>138</sup>. 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 <sup>138</sup>. 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 <sup>138</sup> 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<sup>135</sup><sup>140</sup>. 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 <sup>155</sup> <sup>156</sup> 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 <sup>138</sup>. However, their use carries a higher risk of adverse events and, for obvious reasons, patient reluctance <sup>135 155</sup>. 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 <sup>135 138</sup>.

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 <sup>138</sup>. 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 <sup>135</sup> <sup>138</sup>. 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<sup>157</sup>.

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 <sup>145</sup>. 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 <sup>146</sup> <sup>147</sup>. Several studies have demonstrated its efficacy versus placebo in the treatment of agitation <sup>109</sup> <sup>148</sup> <sup>149</sup>, and other studies are currently underway to compare this formulation with midazolam and aripiprazole <sup>135</sup>. 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 <sup>138</sup> 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 <sup>135</sup>. 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 noninvasive 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 <sup>135 138</sup>. 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 <sup>135</sup>.

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 firstline 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 <sup>135</sup> <sup>138</sup>.

## **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 <sup>158</sup> <sup>159</sup>. 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 <sup>158</sup> <sup>159</sup>.



## 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 <sup>136</sup>. 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 <sup>135</sup>. 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 <sup>50</sup> <sup>160</sup>, and that they can have serious physical and psychological consequences for all the people involved <sup>159</sup>. In addition, if the patient perceives a high level of coercion, this reduces his/her satisfaction with the treatment <sup>161</sup> and may decrease the likelihood that he/she will return to the psychiatric service to continue follow-up and therapy <sup>162</sup> Whatever happens during a crisis is bound to influence the way a patient will perceive the next treatments <sup>163</sup>. 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 <sup>163</sup>. 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<sup>133</sup> and with the spirit of Italian Law No. 180<sup>134</sup>.

#### 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 <sup>135</sup> <sup>138</sup>. 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 <sup>135</sup> <sup>138</sup>.

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 professionals, 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 deescalation
- 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

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