Psychomotor Agitation

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The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) defines agitation as an excessive motor activity associated with a feeling of inner tension. Motor activity is usually non-productive and repetitious and can include behaviors such as pacing, fidgeting, hand wringing, pulling one's clothes, and an inability to sit still. Even if aggression and violence are not core agitation features, a progression in agitation severity can lead to aggressive and violent behaviors. At the first International Experts' Meeting on Agitation, agitation was defined as "a state where patients cannot remain still or calm, characterized by internal features such as hyperresponsiveness, racing thoughts, and emotional tension; and external ones, mainly motor and verbal hyperactivity, and communication impairment".

agitation | bipolar disorder | loxapine | psychomotor agitation | schizophrenia

1. Introduction

Psychomotor agitation (PMA) is characterized by increased psychomotor activity, motor restlessness, and irritability. Individuals with PMA exhibit heightened responsiveness to internal and external stimuli and experience mental tension or altered cognitive function. PMA can occur as a manifestation of a psychiatric disorder (e.g., schizophrenia and bipolar disorder (BD)), central nervous system disease (e.g., Parkinson's disease, Alzheimer's disease or dementia), or substance abuse [1][2]. In the context of BD or schizophrenia, patients experiencing an episode of PMA report feeling uneasy, restless, or nervous and have little success controlling or coping with their agitation [3]. PMA symptom progression usually follows a fluctuating course and can include aggression; however, in all cases, escalation can result in unpredictable, dangerous, and violent behavior that requires a rapid response on healthcare workers and clinicians [4]. Accordingly, prompt recognition and immediate management of PMA symptoms are imperative for decreasing the risk of harm to the patient, healthcare staff, and other individuals in the patient's proximity [5].

2. Epidemiology

Data regarding the epidemiology of PMA are poorly generalizable and mainly derive from studies conducted in specific care settings or patient populations. The reported prevalence of agitation in psychiatric emergency services is between 4–10% [5][6][7]. Moreover, up to 50% of psychiatric emergency service visits involve patients affected by schizophrenia, BD, or dementia, who are patients in which PMA is considered a common symptom in emergency contexts [8][9]. A study in Spain suggested that about 25% of patients with schizophrenia and 15% of those with BD. Experience at least 1 episode of PMA per year, with a median of 2 episodes per year [10].

3. Causes

PMA frequently emerges in psychiatric patients who engage in recreational substance abuse or develop comorbid substance abuse disorder; this phenomenon is especially well-documented in schizophrenia and BD. An estimated 50% of patients with schizophrenia have a comorbid substance abuse disorder [11][12]. Alcohol abuse is another frequent cause of PMA, especially in idiosyncratic reactions, acute intoxication, or withdrawal. Subjects who exhibit PMA associated with alcohol abuse are frequently dependent on the substance and have heavily used alcohol in the long term. PMA can also manifest as the result of mixing alcohol with other substances, resulting in a loss of impulse control and aggressive behaviors.

4. PMA Recognition and Assessment

PMA is an evolving phenomenon for which rapid intervention is essential to avoid escalation to violent behavior. Tools for its evaluation must facilitate quick and easy assessment based only on clinical observation without interviewing the patient. These tools should provide scores and cut-offs to assess PMA severity and inform therapeutic decision-making. The early signs of PMA include changes in different domains [13]. In the presence of one or more of these signs, immediate identification of PMA severity and intervention is necessary to avoid escalation to higher levels:

- Behavioral: inappropriate verbal or motor activity, irritability, impaired self-control, reduced cooperation, aimless wandering, complaining.
- Cognitive: temporal/spatial disorientation, decreased attention, delusion/hallucination, refusal to communicate.
- Physical: weakness, headache, autonomic signs as tachycardia, dyspnea, sweating, tremor, muscle tension.

In order to permit the more standardized assessment of PMA, several rating scales have been developed to assess symptom escalation and agitation severity, including context-specific scales. A number of scales are currently available for use in psychiatric settings (Table 1).

Table 1. Ratings scales for psychomotor agitation in emergency care settings.

Scale	No. Items	Scoring	Total Score Range	Time to Complete
The Agitated Behaviors Mapping Instrument (ABMI)	29 items	1–4	29–203	From 20 min to 1 h observation
The Agitation Severity Scale (ASS)	21 items	0–3	0–63	10 min
The Aggressive Behavior Scale	4 items	0–3	0–12	7 days of observation

Scale	No. Items	Scoring	Total Score Range	Time to Complete
The Agitated Behavior Scale	14 items	1–4	14–50	30 min
The Brief Agitation Measure (BAM)	3 items	0–7 (for the past week)	3–21	Few minutes
The Brief Agitation Rating Scale (BARS)	10 items	0–3	0–30	4 days observation
The Broset Violence Checklist (BVC)	6 items	0–1 absent/present	0–6	Few minutes
The Clinical Global Impression Scale for Aggression (CGI-A)	1 item	1–5	1–5	1–2 min
The Cohen-Mansfield Agitation Inventory (CMAI)	4 domains 29 items	1–7 (for the past week)	29–203	20 min
The Historical, Clinical, and Risk Management-20 Violence Risk Assessment Scheme (HCR-20)	3 domains 20 items	N: No/ P: Possibly/ Y: Yes H: in the last 1–6 months C: current episode R: future risk for 1–6 months	Not applicable	From 30 min to a few hours
The Neurobehavioral Rating Scale-Revised (NRS-R)	5 domains 29 items	0–3	0–87	From 20 min to 1 h
The Overt Aggression Scale (OAS)	4 domains 16 items	0–4	0–16	A few minutes
The Overt Agitation Severity Scale (OASS)	3 domains 16 items	1–4	0–120	15 min observation
The Positive and Negative Syndrome Scale-Excited Component (PANSS- EC)	5 items	1–7	5–35	Few minutes
The McNiel-Binder Violence Screening Checklist (VSC)	5 items	0–1 absent/present	0–5	Few minutes
The Pittsburgh Agitation Scale (PAS)	4 items	0–4	0–16	A few minutes
The Ryden Aggression Scale	26 items	0–5	0–125	20 min
The State-Trait Anger Expression Inventory (STAXI)	44 items	0–4	0–132	5–10 min

Scale	No. Items	Scoring	Total Score Range	Time to Complete
The Staff Observation Scale (SOAS)	4 events	3–10	24–30	10–15 min of event reporting

5. Management Strategies

The management of PMA in emergency care settings largely depends on the severity of patient symptoms and the care context's nature. In general, non-pharmacological management should progress from less invasive or coercive measures to more invasive or coercive measures [14]. In many circumstances, behavioral control methods and de-escalation strategies such as verbal intervention, offering food or beverages, and letting patients smoke or offering nicotine replacement are helpful to manage agitation and prevent its escalation into aggression or violence [15]. Therefore, the approach to an agitated patient should start with environmental modification and verbal de-escalation in a manner that provides physical comfort and minimizes external stimuli. Effective management is significantly influenced by the coordination of this response among healthcare professionals and the ability to enact environmental modification in a timely fashion [16]. To this end, another critical goal during initial de-escalation is to ensure the safety of the patient and those around them (e.g., remove or secure all objects that can be potentially harmful) while respecting the patient's dignity and ensuring that the patient does not feel threatened.

6. Pharmacological Management

Pharmacological strategies for PMA in emergency care settings should control agitation or violent behavior without producing excessive sedation and should preferably avoid invasive administration routes [17]. The pharmacological management of agitation has traditionally employed three classes of medications: first-generation antipsychotics (FGAs), benzodiazepines (BZDs), and second-generation antipsychotics (SGAs) [15]. Available pharmacological tools and emerging treatment options for PMA are outlined below and summarized in Table 2.

Table 2. Parenteral and inhaled pharmacological treatments for psychomotor agitation.

Class	Drug	Mode of Admin	Dose Range (mg)	Adverse Effects	Contraindications	Treatment Associations and Recommendations
FGA	Haloperidol	IM	5–30	• NMS • Extrapyramidal side effects • Torsade de pointes	• Severe cardiovascular disorders • History of seizures • EEG abnormalities	• Lorazepam, promethazine, or diphenhydramine (low risk of NMS) • FGAs should only be administered

Class	Drug	Mode of Admin	Dose Range (mg)	Adverse Effects	Contraindications	Treatment Associations and Recommendations
				• QT prolongation • Falls • Torsade de pointes • Cardiac arrest • Sudden death	• Dementia-related psychosis • Parkinson's disease • Haloperidol hypersensitivity	during pregnancy if the benefit clearly outweighs the potential risk to the fetus • Use with caution in patients < 17 years of age.
	Chlorpromazine	IV	5–20			
		IM	50–150	• Hypotension • Falls • Pain at the site of injection • NMS • Extrapyramidal side effects • Alpha-adrenergic effects	• History of seizures • Dementia-related Psychosis	
		IV	25–50	• Prolonged unconsciousness • Sudden death (for high doses)		
	Loxapine	Inhalation	9.1–18.2	Extrapyramidal side effects	• Asthma • Chronic obstructive pulmonary disease	Evidence of use in minors unavailable

Class	Drug	Mode of Admin	Dose Range (mg)	Adverse Effects	Contraindications	Treatment Associations and Recommendations
	Zuclopenthixol Acetate	IM	50–150	• Fatal cardiac events • Sudden death	• Patients requiring immediate effect onset (delayed onset of about 8 h) • Children and adolescents	
	Promazine	IM	50–300	• Hypotension • Somnolence • Dizziness • Paralytic ileus • Ketoacidosis • NMS	• Coma • Bone marrow depression • Pheochromocytoma • Central nervous system depression • Promazine hypersensitivity	In children ≥ 12 years and adolescents, dosage should not exceed 0.25–0.50 mg/kg
SGA						• Lorazepam • The safety and efficacy of aripiprazole injection have not been established in subjects ≤ 17 years
	Aripiprazole	IM	10–30	• Low risk of extrapyramidal effects • Cardiovascular effects	Cardiovascular disorders	
	Ziprasidone	IM	10–40	• DRESS	Cardiovascular disorders	The safety and efficacy of ziprasidone injection have not been

Class	Drug	Mode of Admin	Dose Range (mg)	Adverse Effects	Contraindications	Treatment Associations and Recommendations
						established in subjects ≤ 17 years
	Olanzapine	IM	10–20	• Hypotension • Bradycardia • Cardiorespiratory depression	• Substance or alcohol abuse • Contraindicated in association with benzodiazepines	• Administration with BDZ. isn't recommended due to safety considerations. • The safety and efficacy of olanzapine injection have not been established in subjects ≤ 17 years
BZD						
	Lorazepam	IM IV	2–8	• Respiratory depression • Ataxia • Excessive sedation • Memory impairment • Paradoxical disinhibition	• Intra-arterial administration • Use in neonates or infants • Acute narrow-angle glaucoma • Severe respiratory insufficiency • Alcohol dependence and abuse • Sleep apnea	• Oral risperidone • Use lower dosages in children and adolescents • Drug of choice for psychomotor agitation in epilepsy
	Diazepam	IV	10–40	• Respiratory depression	• Intra-arterial administration	• Use lower dosages in

Class	Drug	Mode of Admin	Dose Range (mg)	Adverse Effects	Contraindications	Treatment Associations and Recommendations
				• Ataxia • Excessive sedation • Memory impairment • Paradoxical disinhibition	• Use in neonates or infants • Acute narrow-angle glaucoma • Severe respiratory insufficiency • Alcohol dependence and abuse • Sleep apnea	children and adolescents • Useful for psychomotor agitation in epilepsy
Others (when antipsychotics or BDZs are contraindicated)	Sodium valproate	IV	400–1200	• Increased liver enzymes • Hepatotoxicity • Excessive sedation • Ataxia	• Intra-arterial administration • Use in neonates or infants • Hepatic disorders • Porphyria • Coagulopathies • Pregnancy and breastfeeding • Mitochondrial disorders such as Alpers-Huttenlocher syndrome	• IV sodium valproate doesn't have direct psychiatric indications in the product label • Useful for psychomotor agitation in epilepsy

Italicized drugs or modes of administration are not recommended. BZD, benzodiazepine; DRESS, drug reaction with eosinophilia and systemic symptoms; EEG, electroencephalogram; FGA, first-generation antipsychotic; IM,

intramuscular; IV, intravenous; NMS, neuroleptic malignant syndrome; SGA, second-generation antipsychotic.

7. Conclusions

The prompt recognition and management of PMA in emergency care settings and clinical settings remain important healthcare providers' challenges. Differential diagnosis of the underlying cause of the PMA episode and objective grading of its severity are necessary to inform appropriate management. Initial responses include de-escalation and behavioral strategies to calm the patient and make them a cooperative participant in their own care. Invasive treatment modalities (e.g., intramuscular medications) should only be reserved for severe cases of agitation, and when pharmacological intervention is needed, oral or other non-invasive modalities of administration are preferable. Among traditional approaches to the pharmacological management of PMA in emergency care settings, inhaled loxapine is emerging as a beneficial therapy associated with good efficacy, safety, and patient satisfaction.

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