

Review

Etiology, Epidemiology and Common Disorders Associated with Agitation

Doaa Khalid Bajabir ^{1*}, Abdulmalek Alshomrani ², Jumana Alaama ³, Nouriyah Arishi ⁴, Mohammed Asiri ⁵, Arafah Alsayed ⁶, Anmar Alshibely ³, Fayad Mulla ⁷, Musab Alrehaili ⁸, Abdulaziz Adam ⁹, Rawa Alhumaid ¹⁰

¹ Department of Psychiatry, East Jeddah Hospital, Jeddah, Saudi Arabia

² College of Medicine, Baha University, Baha, Saudi Arabia

³ Department of Psychiatry, Eradah Mental Health Complex, Jeddah, Saudi Arabia

⁴ Department of Plastic Surgery, King Fahad Central Hospital, Jazan, Saudi Arabia

⁵ Department of Psychiatry, Eradah Mental Health Complex, Abha, Saudi Arabia

⁶ College of Medicine, Umm Al-Qura University, Mecca, Saudi Arabia

⁷ Department of Psychiatry, Eradah Mental Health Complex, Medina, Saudi Arabia

⁸ Department of Psychiatry, King Salman Medical City, Medina, Saudi Arabia

⁹ Department of Orthopaedics, King Fahad Hospital, Medina, Saudi Arabia

¹⁰ College of Medicine, King Khalid University, Abha, Saudi Arabia

Correspondence should be addressed to **Doaa Bajabir**, Department of Psychiatry, East Jeddah Hospital, Jeddah, Saudi Arabia.
Email: doaabj@gmail.com

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Abstract

Agitation is a frequent clinical condition that notably raises the hospital morbidity. It generally coexists with a wide range of mental and cognitive symptoms and has a diverse clinical course. Agitation is a state of extreme restlessness or irritability including excessive muscular activity accompanied by a sense of inner strain and exceeding restlessness associated with mental discomfort. It occurs frequently in psychiatric units, emergency rooms, and nursing care homes, and is a common condition experienced by the patients especially of neuropsychiatric diseases. Agitation is the third most prevalent neuropsychiatric symptom in dementia, behind apathy and depression, with an overall approximate prevalence of 30%. Agitation has variable prevalence as per the diseases. The purpose of this research is to review the available information about the etiology, epidemiology and common disorders associated with agitation. Trauma particularly to the head, widespread infection, sepsis, dementia, delirium, exposure to toxins, electrolyte imbalances, endocrine abnormalities, and a post-ictal state is one of the risk factors for agitation. Agitation prevalence varies between 30% and 50% in Alzheimer's disease, accounts for 30% in dementia with Lewy bodies, 40% in frontotemporal dementia, and 40% in vascular dementia, as per the various studies. Agitation is a broad category of unrelated behaviours that frequently changes course and is visible in a range of clinical settings. Several underlying pathophysiologic conditions are mediated by dysregulations of the dopaminergic, serotonergic, noradrenergic, and GABAergic systems. Further research will be helpful in defining new management strategies.

Keywords: agitation, prevalence, dementia, disease

Introduction

Agitation is defined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition as an excessive motor activity accompanied by an inner tension or strain. Including motor activity, which includes actions like pacing, fidgeting, hand wringing, pulling one's clothes, and being unable to sit still, is typically unproductive and repetitive. Aggression and violence can result from increased agitation severity even if these traits are not the basis of agitation (1, 2). Agitation was described as a state where patients cannot persist calmness, marked by intrinsic features such as hyperresponsiveness, racing thoughts, and emotional tension; and external ones, primarily motor and verbal hyperactivity, and communication impairment at the first International Experts' Meeting on Agitation (3).

In patients with severe psychiatric diseases such as schizophrenia, schizoaffective disorder, and the manic phase of bipolar disorder, agitation refers to a variety of symptoms and behavioural patterns. There are many degrees of agitation, ranging from mild to severe, with quick fluctuations, which can quickly progress to aggressive conduct. Acute agitation episodes typically necessitate psychiatric emergency visits, admission to an inpatient mental institution, and ongoing treatment. Agitation may result from the underlying disease's natural course or from a patient's failure to take their prescribed long-term medicine as directed. In individuals with underlying psychotic disorders, there are additional risk factors for agitated behaviour that may or may not be present during each episode of acute agitation. There may also be concomitant illnesses caused by iatrogenic factors or disorders of substance use (4).

Agitation is a common clinical issue that significantly increases hospital morbidity. Agitation typically occurs in conjunction with a complex constellation of cognitive and mental symptoms and has a variable clinical trajectory. The observation of symptoms that are incredibly diverse and present at various times causes major underlying diseases to be misdiagnosed or not recognized. Agitation is most frequently brought on by delirium, dementia, and acute psychosis. Hospitalization risk factors include discomfort, anxiety, and stressors common to intensive care. Multiple factors may contribute to agitated states, and each one needs to be investigated and handled separately. A thorough history, patient observation, a physical exam, and only the most pertinent diagnostic tests are used to make a final diagnosis (5).

The interplay of triggering circumstances and patient features can result in a complex etiology for aggression or behavioural instability. Agitation, often referred to as high motor activity or inner restlessness, can be a symptom of an underlying ailment or be a normal physiological response to a particular environment. New environments, drug intoxication or withdrawal, alcohol use, and general medical disorders are the leading causes of agitation. Trauma particularly to the head, widespread infection, sepsis, dementia, delirium, exposure to toxins, electrolyte imbalances, endocrine abnormalities, and a post-ictal state are a few of the prevalent medical diseases causing agitation. Agitation may be caused by mental health issues such as anxiety, depression, bipolar disorder, autistic spectrum disorder, and substance abuse (6). The purpose of this research is to review the available information about the etiology, epidemiology and common disorders associated with agitation.

Methodology

This study is based on a comprehensive literature search conducted on August 15, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about the etiology, epidemiology and common disorders associated with agitation. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Agitation is a generalized cluster of unconnected actions that typically exhibits a changing trajectory and can be observed in a variety of clinical circumstances. Dopaminergic, serotonergic, noradrenergic, and gamma-aminobutyric acid system dysregulations are mediators of a variety of underlying pathophysiologic disorders. These pathophysiologic anomalies lack recognizable clinical characteristics. There is no unified etiologic pathophysiology, despite the possibility of a final common mechanism. It is important for the clinician to treat the overarching psychiatric problem with addressing the underlying pathophysiology as well. Regardless of the cause of the agitation, medications that decrease dopaminergic or noradrenergic tone or boost serotonergic or gamma – aminobutyric acid tone will typically lessen it (7). A common clinical symptom of

many neuropsychiatric diseases is agitation. It is a typical symptom of dementia syndromes such as dementia with Lewy bodies, frontotemporal dementia, and Alzheimer's disease. It manifests in depression, bipolar disorder, and schizophrenia. Aggression is not the same as agitation, which can happen without aggression even if agitation may contain violent behaviours including pacing, rocking, repetitious mannerisms. Agitation can lead to institutionalization, reduce the quality of life for patients and carers, and, in more severe cases, necessitate medication management. There is a developing biology of agitation, and clinical and neuroimaging research both link frontal brain dysfunction to the condition. In the management of patients with cognitive impairment, there is an unmet need for the treatment of agitation, both pharmacologically and non-pharmacologically (8).

Epidemiology of Agitation

Global systematic review findings reported wide range of prevalence rates from 5% to 88%, with regional variations in rates. Lower ranges were observed in Asia. Detailed illustration of prevalence of agitation is depicted in (Figure 1) (9). Findings of an American

study reported that based on the primary agitation phenotype, 24.9% cases of agitation were reported. Longer hospital stays were correlated with severe symptoms, with an increase in stay of 0.9 days for every 10% increase in agitation phenotype (10). German study reported that severe agitation was noticed in 6.3% of the population. The largest correlations were found for euphoria and jubilation (odds ratio (OR) 7.6, Confidence Interval (CI) 3.1-18.5), delusions (OR 7.3, CI 4.0-13.2), apathy or indifference (OR 2.8, CI 1.7-4.7), anxiety (OR 2.2, CI 1.2-3.8), night-time activities (OR 2.4, CI 1.4-4.2), motor disturbances (OR 2.4, CI 1.4-4.1), and male sex (OR 2.4, CI 1.3-4.2) (11). In psychiatric emergency services, agitation is reported to occur 4%–10% of all the time. Additionally, patients with schizophrenia, bipolar disorder, or dementia those in whom psychomotor agitation is thought to be a frequent symptom in emergency contexts make up to 50% of visits to psychiatric emergency services (12). According to a Spanish study, 15% of people with bipolar disorder and 25% of schizophrenia patients experience at least one psychomotor agitation episode annually, with a median of two episodes (13).

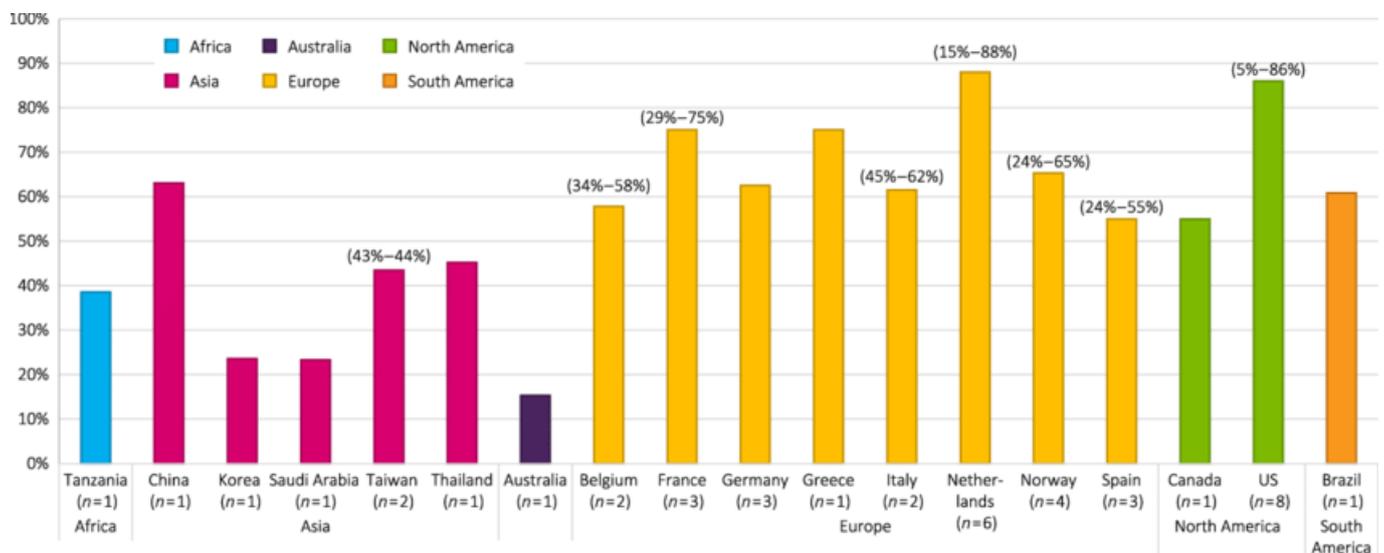


Figure 1: Prevalence of agitation as per geographical region

Findings of a prospective observational study reported that agitation was observed in 2.6% of the study population. Agitated patients frequently required restraint and sedation, with large rates of clinical events needing intervention (14). Results of a retrospective database study showed that during the observation period, reported prevalence of agitation was 44.6% among the population. Only 5% of individuals with agitation had behavioural disturbance listed as a

diagnostic code, 31.4% and 41.3% of patients with agitation, preindex and post index, falling 22.6% and 21.7%, and restlessness 18.3% and 23.3% were the most frequent symptom categories. Agitation prevalence was 61.3% among the 78 827 patients (24.6%) with known Alzheimer's disease /dementia severity. Moderate-to-severe and severe Alzheimer's disease /dementia patients were more likely to be agitated during the observation period 74.6% and 68.3%, respectively, while patients

with mild disease were less likely to be agitated (56.4%) (15).

Chinese observational survey reported that agitation was prevalent in 853 of 1400 people (60.92%) and 826 of 1400 people (59.00%), respectively as per the Positive and Negative Syndrome Scale-Excited Component and Behavioural Activity Rating Scale. Overall, agitation was present in 47.50% of cases (665 of 1400). Being aggressive at baseline (with the Modified Overt Aggression Scale score > 4 , OR=6.54; 95% CI =4.93-8.69) was the most significant risk factor for agitation. Other risk factors included a history of violent behaviour, residing in a northern region, being hospitalized against one's will, the severity of the disease, a poor level of education, being alone at home, being unemployed, or being retired (16). Results of an Australian study showed that 59 distinct agitated behaviours were identified in the study group. There was no difference in the prevalence of dementia between male and female patients (44.1%), between urban and rural facilities (42.1% [standard deviation = 17.9%], or between dementia and agitation (76.5% [standard deviation = 18.4%]). The top 10 behaviours were pushing, whining, getting frustrated, roaming, speaking in an obnoxious voice, refusing, pacing, restlessness, pushing, and shouting. In 53% of those with dementia agitation, four to seventeen agitated behaviours coexisted, indicating considerable caregiver burden in these residential aged care facilities (17).

Agitation associated disorders

Increased, frequently undirected motor activity, restlessness, aggression, and mental distress are all characteristics of agitation which is a behavioural syndrome. Agitation prevalence varies between 30% and 50% in Alzheimer's disease, 30% in dementia with Lewy bodies, 40% in frontotemporal dementia, and 40% in vascular dementia, according to multiple studies in literature. Agitation is the third most prevalent neuropsychiatric symptom in dementia, behind apathy and depression, with an overall prevalence of roughly 30%. In nursing home residents, it is even more prevalent accounting for approximately 80%. The anterior cingulate cortex and orbitofrontal cortex, which are important in selecting the salient stimuli and subsequent decision-making and behavioural reactions, are primarily involved in the pathophysiological mechanism producing agitation (18).

More than 90% of dementia patients suffer behavioural or neuropsychiatric symptoms at some point throughout their illness. These symptoms include agitation,

psychotic symptoms including hallucinations and delusions, apathy, sadness, and sleep difficulties. It has been estimated that 76% of people with Alzheimer's disease and 60% of those with mild cognitive impairment experience agitation. There is currently no Food and Drug Administration-approved pharmacologic treatment for agitation in dementia, despite the fact that treatments that are known to affect relevant pathways are frequently used, have been shown to be associated with decreases in cholinergic and serotonergic markers. Antipsychotics, acetylcholinesterase inhibitors, antidepressants, anticonvulsants, and antidepressants are now used as pharmacologic therapies for dementia-related agitation. A thorough, individualized treatment approach with both pharmacologic and non-pharmacologic therapies is advised by the 2016 American Psychiatric Association Practice Guidelines, with antipsychotics being indicated when agitation symptoms are severe (19).

Agitation affects the length of stay and functional results for 70% of patients with traumatic brain injury who are hospitalized. Pharmacological and behavioural therapies are used during treatment. In intensive care or rehabilitation settings, there has been a lot of research on traumatic brain injury agitation. The management of agitation in traumatic brain injury patients in acute care units might be difficult for medical personnel. Utilizing the resources at hand, innovative strategies are required to achieve outcomes (20). Mussele et al. stated that more severe frontal lobe, behavioural, and depressive symptoms were present in patients with agitation. In contrast to non-agitated Alzheimer's disease patients, all behavioural symptoms and agitation types were more severe in agitated Alzheimer's disease patients, although only diurnal rhythm abnormalities were present in agitated mild cognitive impairment patients. As a result, patients with agitation had more severe Behavior-Alzheimer's disease global scores than patients without agitation. Mild cognitive impairment patients with agitation displayed more severe behavioural and depressive symptoms than Alzheimer's disease patients without agitation when mild cognitive impairment and Alzheimer's disease patients were compared. In contrast to mild cognitive impairment, the organization of agitation in AD included both physically aggressive and non-aggressive conduct (21).

Trzepacz et al. described in their findings that neuropsychiatric inventory Alzheimer's patients and moderate cognitive impairment-converter patients both had worsening scores on the agitation and aggression

subscales. Greater atrophy of the frontal, insular, amygdala, cingulate, and hippocampal areas of interest was linked to more severe agitation and aggression. Only mild cognitive impairment-converters for the posterior regions of interest in a mixed-effect model repeated measures analysis showed Mini-Mental State Examination score to be significant. Aggression and agitation were not linked to demographics or apolipoprotein. Aggression is linked to neurodegeneration in the anterior salience network, which may lessen the ability to comprehend and regulate behaviours, in Alzheimer's disease and moderate cognitive impairment (22).

Sachs et al. stated that agitation has been measured in many clinical situations using a variety of devices and recent medical literature. The treatment of agitation as a distinct entity in many mental diseases has been subpar. Many people with schizophrenia, bipolar mania, or dementia experience agitation on a regular basis. Additionally, agitation has a negative impact on many aspects of the healing process, such as direct patient care, the strain on caregivers, and community resources. Agitation has been associated with frontal brain dysfunction and mutations in the catechol-methyltransferase gene, which is implicated in catecholamine inactivation and dopamine metabolism. Patients with dementia are more likely to become agitated due to cognitive impairment and neurological dysfunction. Agitation may be linked to both frontal and temporal lobe dysfunction in people with Alzheimer's dementia (23). Literature reveals the definite and strong association of agitation with the neuropsychiatric diseases and remains a significant challenge for clinicians, further clinical research including clinical trials, population based cohort studies will assist in developing new management and treatment modalities and recommendations, it will also be beneficial in studying the causes and risk factors for agitation since the available literature is quite scarce regarding the etiological profile of agitation. Population -based surveys can be utilized to define and the general prevalence of agitation.

Conclusion

Agitation remains a prevalent condition among patients especially suffering from neuropsychiatric diseases. Management of agitation poses a great challenge to healthcare and often involves multidisciplinary team; further clinical research can aid in defining effective guidelines and recommendations for the management and treatment of agitation.

Disclosure

Statement

The authors declare no conflict of interest.

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Ethical consideration

Non-applicable.

Data availability

Data that support the findings of this study are embedded within the manuscript.

Authors' contribution

All authors contributed equally to the drafting, writing, sourcing, article screening and final proofreading of the manuscript.

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