

Review Article

Delirium: Issues in diagnosis and management

F. K. Salawu, A. Danburam, P. Ogoalili¹

Neurology Unit, Department of Medicine. Federal Medical Centre, Yola, Nigeria, ¹Federal Neuropsychiatry Hospital, Maiduguri, Nigeria

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Correspondence to: Dr. Fatai K. Salawu, Department of Medicine, Federal Medical Centre, Yola, Adamawa State, Nigeria. E-mail: dr_abdulsalawu@yahoo.com

Abstract

Delirium is a disturbance of consciousness, cognition and perception that occurs frequently in medically ill patients. Although it is associated with increased morbidity and mortality, it is often not recognized and treated by physicians. Literature searches were conducted using MEDLINE with the following keywords/ phrases: *delirium*, *acute confusion* and *management*. Additional articles identified by hand-searching in major journals of medicine and psychiatry, and a review of references cited within these sources supplemented the search. In this article, the available published literature regarding the diagnosis, prevention and treatment of delirium is systematically reviewed. Prevention and treatment strategies do not need to be complex or expensive but require well-coordinated interventions from multiple disciplines, including nursing, psychiatry, neurology and primary care, as well as the cooperation and significant effort of family and friends. Atypical antipsychotic agents offer some advantages over haloperidol and in a limited number of studies appear safe and effective for delirium.

Keywords: Acute confusional state, delirium, disorientation, hallucination, management

Résumé

Délire est une perturbation de conscience, cognition et de perception qui se produit fréquemment en médicalement malades. Même s'il est associé à une augmentation de la morbidité et mortalité, il est souvent pas reconnu et traité par les médecins. Littérature recherches ont été effectuées en utilisant MEDLINE avec les mots clés/phrases suivantes: *délire*, *confusion aiguë*, et de *Gestion*. Articles supplémentaires identifié à la main dans les grandes feuilles de médecine et de psychiatrie, la recherche et d'un examen des références citées dans ces sources complété la recherche. Dans cet article, le disponible publié littérature concernant le diagnostic, la prévention et traitement de délire est systématiquement examiné. La prévention et stratégies de traitement ne doivent pas être complexes ou onéreux mais nécessite interventions bien coordonnées de plusieurs disciplines, y compris les soins infirmiers, psychiatrie, neurologie et de soins primaires, ainsi que la coopération et effort important de la famille et amis. Agents antipsychotiques atypiques offre certains avantages sur Halopéridol et dans un nombre limité d'études s'affichent sans danger efficace et de délire.

Mots clés: délire, aiguë confusional État, hallucination, désorientation, gestion des

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Introduction

Delirium is an acute-/subacute-onset neuropsychiatric illness that results in decreased cognitive function accompanied by circadian rhythm disturbances. Although not necessary for a diagnosis of delirium, other symptom clusters suggestive of

classic "psychiatric" illness, such as depression, anxiety and psychosis, frequently co-occur with cognitive impairment and neurovegetative disturbances. The word *delirium* is derived from the Latin term meaning "off the track." This syndrome was reported during the time of Hippocrates, and, in 1813, Sutton described delirium tremens.

Partially due to its heterogeneous nature, delirium is frequently underdiagnosed in clinical practice.^[1] Although often confused with dementia, which is a progressive and degenerative condition marked by gradual and broad cognitive deterioration, delirium is often a temporary condition involving confusion and disorientation.^[2] Historically delirium has also been referred to as acute confusional state, acute organic brain syndrome or toxic psychosis.

Definition of delirium

The word *confusion* is frequently used in common speech, both by professional caring staff and nonprofessional individuals. However, it is seldom defined. It is used synonymously with conditions such as disorientation, inability to think clearly and coherently, clouding of consciousness or some degree of mental disorder. Moreover, more than 60 synonyms of *delirium* have been found in the literature.^[3] It has been suggested that “acute confusional state” (ACS) should be the only accepted synonym for delirium.^[4,5] In the 1987 edition of the *DSM-III-R*,^[6] however, the criteria for delirium were more specific than those in the fourth edition published in 1994. Lipowski^[5] stated in 1992 that there was no consensus on how to define or measure delirium. However, in the past decade, instruments have been developed for measuring delirium. In many studies, delirium has been defined in accordance with the DSM criteria.^[3,7-12] Delirium is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*,^[2] as one of the cognitive disorders; that is, the “core” clinical deficit is in cognitive function. The *DSM-IV-TR* criteria for a diagnosis of delirium include the following 4 items:

- Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention
- A change in cognition (such as memory deficits, disorientation or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia
- The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day
- There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

For classification purposes, *DSM-IV-TR* further specifies delirium types based on etiology. All of these feature the clinical findings mentioned above but differ in the clinical context and putative

cause(s) of the onset of delirium: (1) delirium due to a general medical condition (includes cases due to the physiological effects of a medication); (2) delirium due to multiple etiologies (including multiple general medical conditions, multiple medications or a combination); (3) substances of abuse; (4) substance-withdrawal delirium (substances of abuse); (5) delirium not otherwise specified (cause[s] not confidently identified/classified).^[2] *DSM-IV-TR* has additional codes for the co-occurrence of delirium and dementia.^[2]

Risk factors and causes

In several studies, a variety of factors have been found to relate to delirium. The multifactorial nature is often underestimated, but studies that have accounted for the possibility of multiple causes have found that between 2 and 6 factors may be present in any single case.^[13] Attempting to identify and treat a single cause is overly simplistic; each case needs detailed, repeated assessment for multiple potential factors. Delirium is caused by factors in the patients as well as by pharmacological and environmental factors. Age, preexisting cognitive impairment, severe comorbidity, and exposure to medication are robust predictors of delirium.^[14-16] Models of causation that quantify the role of predisposing factors and precipitating insults have shown that cumulative interactions with baseline risk are especially predictive. Among baseline vulnerabilities to delirium, preexisting central nervous system disease is the most important to the neurologist. If vulnerability at baseline is low, patients are resistant to delirium despite exposure to significant precipitating factors; but if vulnerability is high, delirium is likely to occur with exposure to only minor precipitating factors.^[16] Lipowski^[4] identified 3 classes of risk factors for delirium: predisposing, facilitating and precipitating factors. Three general *predisposing* factors have been established: 60 years of age or older, brain damage (e.g., cognitive impairment) and chronic brain disease.^[4] A uniform finding is that older patients are at higher risk of postoperative delirium,^[17,18] as are patients with preexisting cognitive impairment and/ or dementia,^[17,19,20] epilepsy,^[5] malignancy^[4,5,21] and high systolic blood pressure.^[20] Further, male sex^[11,22,23] and the existence of several medical diagnoses^[22] have been reported as predisposing factors for delirium. The use of psychoactive drugs^[17] or other drug reactions,^[5,24] especially anticholinergic drugs,^[10,25] have been associated with delirium. Several studies have demonstrated that vascular diseases of the brain, for example, stroke and transient ischemic attacks (TIAs), are precipitating organic factors for the development of delirium,^[26] as are

infectious diseases,^[5,18,27,28] especially urinary tract infections.^[10,29] Some of the other common infections of great importance in this environment include malaria, pneumonia, meningitis, typhoid, human immunodeficiency virus–related brain infections and other pyrexias of unknown origin. Patients still needlessly die from delirium from various causes in Nigeria.^[30-33] However, a given pathogenic factor need not be sufficient to precipitate delirium. Predisposing and facilitating factors also co-determine onset, severity and duration.^[4] Francis and colleagues^[34] classified the possible causes of delirium into 8 categories (drug-induced, infection, fluid-electrolyte or metabolic disturbances, intracranial process, low perfusion, alcohol and drug withdrawal, and sensory/ environmental causes). It has been suggested that psycho-social factors alone, such as depression, psychological stress and pain, may precipitate delirium.^[35] However, Lipowski^[4] has stated that it is not clear whether predisposing and facilitating factors can induce delirium in the absence of precipitating organic factors.

Epidemiology

The reported incidence and prevalence rates of delirium during hospitalization ranged from 0% to 85% in a review by Forman.^[36] In another review of postoperative delirium, incidence was 0% to 74%.^[37] Among medical and surgical general hospital inpatients, 10% to 18% became delirious at some point during their hospital stay.^[4,38] At a general surgery department, the incidence rate was 18%;^[39] and at an intensive care unit, 70%.^[40] At general medical departments, the reported incidence rates ranged from 5% to 48%.^[41-43] Furthermore, patients undergoing elective cardiac surgery displayed a delirium incidence of 14%;^[44] and those undergoing major elective surgery, 11%.^[45] In some studies, the incidence of delirium was reduced because of interventional programs related to hip surgery or in other care settings.^[29,46] Cole and colleagues^[47] stated that intervention studies designed to prevent delirium have methodological problems because of the heterogeneity of the patient populations and interventions. They suggest that preventive intervention trials should be conducted with target populations specified by age, level of cognition, severity of illness, and other risk factors for delirium.^[47]

Pathophysiology

The mechanism of delirium still is not fully understood. A classic paper by Engel and Romano^[48] in 1959, reprinted in 2004, memorably described delirium as a “syndrome of cerebral insufficiency.”

As such, one can posit that many possible causes act simultaneously in most cases.^[48] Delirium results from a wide variety of structural or physiological insults. The current pathophysiological model to explain delirium consists of simultaneous cholinergic deficit and dopamine excess as the most validated notable neurotransmitter disturbances;^[49] however, these alterations in acetylcholine and dopamine levels are best regarded as part of a more global derangement of multiple neurotransmitter systems.^[1,50-53] Exposure to anticholinergic medications and higher serum anticholinergic levels correlate with the onset of delirium.^[52] The use of anticholinergic medications has been shown to increase the risk of delirium following stroke.^[50] Dementia highly predisposes to episodes of delirium, while cholinesterase inhibitors to treat dementia may improve symptoms of delirium.^[1,52,53] Gaudreau and Gagnon^[51] present a synthesis of neurotransmitter alterations in delirium, which also highlights interactions of cholinergic and dopamine systems with glutamergic and gamma aminobutyric acid pathways. They propose a model of thalamic gating in delirium that may partially account for the simultaneous cognitive and psychotic symptoms seen in delirium. Another proposed mechanism in delirium is the presence of widespread oxidative metabolism in the brain.^[52] Burns and colleagues^[1] described two neuronal networks in different anatomical sites as important in delirium. The first network diffusely involves the thalamus and both cortical hemispheres, while the other involves the frontal and parietal cortex in the right hemisphere.

Motric subtypes

Delirium can be separated into clinical subtypes based on the level and persistence of motoric activity.^[52,54] Hyperactive is characterized by motor overactivity, frequently described as agitation or anxiety by medical personnel.^[52] These patients are especially likely to exhibit agitation late in the day and overnight. Because of the tendency of these patients to disrupt the care environment, they are more readily identified than hypoactive-delirium patients.

Hypoactive delirium, in contrast, features profoundly decreased motoric activity. Even though some evidence suggests that hypoactive delirium is associated with a worse prognosis than the hyperactive subtype,^[52] hypoactive cases may generate less clinical concern (because these patients are not as disruptive). These patients are frequently misdiagnosed as being “just depressed.”^[52] The distinction between depression and hypoactive delirium requires demonstration of the cognitive and circadian disturbances characteristic of delirium in the hypoactive delirium cases. In addition,

hypoactive delirium cases may be missed when diagnostic criteria for delirium focus on hyperactive symptoms, as compared with the more inclusive nature of the *DSM-IV-TR* criteria.

In mixed delirium, individuals display variable elements of hyperactive and hypoactive delirium at different points of time within a single episode of delirium. This has been reported to be the most common subtype.^[52] A “normal” psychomotor delirium, where psychomotor activity is not affected by delirium, has also been described.^[52]

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Psychiatric differential diagnosis

The psychiatric differential diagnosis of delirium is broad, as a myriad of psychiatric symptoms can manifest in delirium cases; for example, the patient may appear depressed, anxious, agitated, psychotic, or primarily cognitively impaired or a combination of these.^[55] The “acute” psychiatric presentation of a patient in delirium, for example, psychotic, depressed or anxious, is not indicative of an ongoing psychotic, mood or anxiety disorder and can be conceived of as an “acute” consequence of the delirium itself.

The psychotic symptoms in delirium (hallucinations and delusions) tend to fluctuate throughout the course of an episode of delirium and are accompanied by cognitive deficits, while psychotic disorders are more persistent and less likely to be concurrent with cognitive impairment.^[52] Lewy body dementia, which features psychotic symptoms and a fluctuation in cognitive status as part of its dementia syndrome, is challenging to distinguish from delirium.^[55] Intoxication or withdrawal from substances of abuse can cause maladaptive behavioral changes (including anxiety, mood, psychotic and cognitive symptoms) that do not necessarily meet full criteria for delirium (especially if the symptoms do not have a waxing and waning course and are not associated with circadian disturbances).

Prognosis

Prognosis for delirium can be grim, as delirium is associated with increased morbidity and mortality, increased hospital length of stay, longer postoperative recovery periods, long-term disability and increased rate of institutionalization.^[1,52,54-58] Patients who develop delirium during hospitalization have a mortality rate of 22% to 76% and a high rate of death during the months following discharge.^[15] The natural history of delirium can be hard to quantify; since, once recognized, patients ideally receive prompt evaluation and care, such that the

“natural history” of untreated delirium in a modern medical setting is a bit of a misnomer. In a review, Weber and colleagues^[58] summarized that delirium typically resolves in 10 to 12 days.

Evaluation

Diagnosis and management in delirium are simultaneous and continuous processes, with frequent reassessment of progress being an integral part of management.^[55] Evaluation of delirium should include review of medical and psychiatric history, review of prescription and over-the-counter medications, and alcohol and other substance abuse history.^[52] Physical examination should address all the possibly implicated systems described above, and the mental status examination needs to be detailed, including assessment of orientation, memory/concentration, naming, attention, language use, mood/affect and assessment of psychosis.

Most of the standardized observational methods of measurement and assessment of cognition by validated instruments such as the confusion assessment method, Folstein mini-mental state examination (MMSE), delirium rating scale (both original and revised versions DRS and DRS-98), confusional state evaluation, and memorial delirium symptom interview are recommended,^[52,54,55,59,60] but they are culturally insensitive, socioeconomically and educationally biased and have not been found suitable for use in Nigeria communities. However, Baiyewu and colleagues^[61] modified the MMSE to take into consideration the culture and educational status of the Nigerian adults, among whom illiteracy rate is still high. Other bedside assessments of cognitive functions such as sustained attention, clock drawing, fund of knowledge, cognitive estimations, ability to make abstract connections, category generation, as well as response inhibition tests, indicate that these functions may be impaired in delirium.

The diagnosis of delirium is clinical. No single test is successful. Laboratory studies to consider routinely include serum electrolytes, chemistry panel, liver-associated enzymes, ammonia, complete blood count, urine drug screen, blood alcohol, thyroid-stimulating hormone, calcium, magnesium, phosphate, pulse oximetry and urinalysis. Any suspicion of infection should lead to cultures of urine, blood and sputum as needed. Radiological studies include chest x-ray and unenhanced computerized tomography of the head. Other studies to consider, depending on the clinical circumstances, include arterial blood gases, cerebrospinal fluid analysis, human immunodeficiency virus, and hepatitis serology. Electroencephalography is not routinely

indicated but may help in equivocal cases, as it presents with diffuse bilateral slowing in most cases of delirium.^[1,54]

Management

Prevention

Ideally, patients at high risk for delirium should be identified and preventive strategies employed. Weber and colleagues⁵⁸ reviewed the literature on clinical trials to prevent delirium and summarized that the following courses of action have been shown to be helpful: interventions to correct circadian disturbances; nursing staff education; cognitive screening; limiting physical immobility; avoidance of sensory deprivation; prevention of dehydration; advice from geriatrics consultants, geriatric specialty nurses and psychogeriatricians; and a scheduled pain management protocol. Preoperatively, psychological support may decrease the risk for later postoperative delirium.^[55] Despite the relative scarcity of good evidence on prevention of delirium in developing countries, where infection plays a significant role in causation of delirium, it is unclear to what extent vaccination, aggressive management of malnutrition and hygienic midwifery would benefit a patient. It is not advisable to recommend specific preventive intervention with the widespread availability of over-the-counter antibiotic treatment in Nigeria, but it is likely that personal and domestic hygiene advice will be relevant to contain common problems such as malaria. The alternative to prophylaxis in resource-poor areas is prompt recognition and re-treatment of recurrent episodes using appropriate antibiotic, and patients must be warned of the possible significance of a recurrent febrile illness and be re-investigated.

Nonpharmacological intervention

The most important intervention for managing delirium is correction of the underlying systemic condition(s) responsible for the delirium.^[54] The inpatient management of the delirious patient requires several nonpharmacological measures. Frequent vital signs and nursing assessments assure that nursing personnel will reassess the patient to document behavioral safety, monitor intake and output status and describe the sleep-wake cycle. Restraints are routinely needed for combative/physically dangerous delirious patients.

Private, rather than shared, hospital rooms may help decrease stimulation.^[55] Orientation devices such as prominently displayed clock, calendar and television news programming may help to reorient the patient.^[55]

Provision of adequate lighting with daily changes in the ambient lighting level to promote a normal

circadian rhythm may be useful.^[55] In intensive care units, delirious patients may become confused by medication equipment and may use a piece of equipment as a weapon. In addition, noises of the hospital may compromise an already disordered sleep-wake cycle. Assessment of swallowing function may be necessary before oral feedings are allowed.^[52] Close monitoring of fluid-electrolyte status and respiratory and cardiovascular status is critical.^[52]

After recovery, delirious patients may recall fragments of the delirium episodes, which often produce anxiety.^[52] Psychoeducational interventions to normalize and/ or reconstruct experiences of delirium may prove helpful to recovery. Later recall of events by patients during an episode is variable.^[1] In a study of 154 delirium patients, 53.5% were later able to recall their delirium experience.^[62] Delirium severity, perceptual disturbances and short-term memory impairment were the variables most notably associated with later poorer recall of delirium.^[62] The majority of patients who recalled their episode described delirium as highly distressing; and spouses, caregivers and nurses reported episodes of delirium as highly distressing.^[62]

Pharmacological intervention

Drug treatment of delirium requires careful consideration of the balance between the effective management of symptoms and potential adverse effects. The United States Food and Drug Administration (USFDA) have specifically approved no pharmacological agents for delirium. Palliative or symptomatic treatment is sometimes necessary to make a patient comfortable. Pharmacotherapy consists primarily of the judicious application of psychotropic drugs developed for other psychiatric conditions, with some nuances specific to this challenging condition.

Typical antipsychotics

The best-established medications for delirium are the typical antipsychotics; generally, the most practical is haloperidol.^[52,55,58] Antipsychotics are indicated for delirium episodes regardless of motor subtype and generally improve cognitive function because they contain aberrant motor behavior, decrease psychotic symptoms and promote normalization of the sleep-wake cycle.^[55] Haloperidol is chosen primarily because of its classification as a high-potency antipsychotic as it has high potency for D₂ receptor blockade, produces fewer blockades of acetylcholine receptors and causes less orthostatic hypotension than other typical antipsychotics.^[52,54,55] As such, it is appealing as an intervention for delirium, which is modeled as an acetylcholine-deficient and hyper-dopaminergic

state. Low dose of oral haloperidol (1-10 mg/day) improves symptoms in most patients. Elderly and hypoactive delirium patients can be started at doses of 0.5 to 1 mg every 12 hours. Prompt response to treatment and frequent adjustments of the doses are the rule, not the exception, in managing delirium with haloperidol.^[55] The risk for extrapyramidal symptoms (EPSs) attributable to haloperidol is less with the intravenous than the oral or intramuscular delivery because the hepatic “first pass” is avoided.^[55] QT corrected for heart rate (QTc) prolongation has been reported with haloperidol; therefore, pre-treatment electrocardiography (ECG) and regular ECG monitoring are needed.^[63] A QTc of greater than 500/ms at baseline or treatment-emergent makes *torsade de pointes* more likely and calls for a discontinuation of haloperidol.

Atypical antipsychotics

There is growing recent literature on the use of atypical antipsychotics for delirium.^[52,54,55] Owing to their common mechanism of action of variable D₂ receptor blockade and concurrent blockade of the 5-hydroxytryptamine (5-HT)₂ receptor, they all carry less risk for sedation and EPSs than haloperidol and other high-potency typical antipsychotic agents.^[54,55,64] Mittal and colleagues^[65] treated 10 delirium patients with a mean dose of 0.75 mg/d of risperidone and found improvement in cognitive and behavioral symptoms; no patient experienced EPSs. Parellada and colleagues^[66] treated 64 delirium patients with a mean dose of 2.6 mg/d of risperidone; 90% improved, and only 3% experienced adverse events, none of which was EPSs. Han and Kim^[67] completed a double-blind study of risperidone (1.0 mg/d) and haloperidol (1.5 mg/d) for delirium in 28 patients and found no significant difference in efficacy or response rate between the two agents. Isolated cases of delirium apparently having been induced by risperidone have been reported, so caution is warranted.^[68-71] Sipahimalani and Masand^[72] treated 11 delirium patients with olanzapine (mean dose, 8.2 mg/d) and 11 with haloperidol (mean dose, 5.1 mg/d) and found similar rates of clinical improvement (5 olanzapine and 6 haloperidol patients with “marked” improvement). A prospective trial of olanzapine in 79 delirious cancer patients revealed 76% of cases with complete resolution of delirium; 30% of cases experienced sedation.^[64] Among several variables examined, age over 70 was the variable most highly associated with a poorer response to olanzapine. Sasaki and colleagues^[73] treated 12 delirium patients with quetiapine (mean dose, 44.9 mg/d) and found that all patients achieved remission of delirium symptoms with no excess sedation or EPSs. Torres and colleagues^[74] successfully treated 2 delirium cases with quetiapine (doses were 50

mg/d and 25 mg/d, respectively) without adverse effects. Leso and Schwartz^[75] successfully treated delirium with ziprasidone (100 mg/d) in a patient at risk for movement disorders as an effect of risperidone; the patient however experienced an 8.4% increase in QTc plus premature ventricular contractions, necessitating eventual discontinuation of ziprasidone. None of the atypical antipsychotics is available in intravenous form, although risperidone, olanzapine and ziprasidone are available in intramuscular form.

Benzodiazepines

Benzodiazepines have two roles in the management of delirium. In case of delirium due to multiple causes or a single cause other than alcohol or benzodiazepine withdrawal, benzodiazepines are an adjunctive to antipsychotics.^[55] They are also a useful adjunctive treatment for patients who cannot tolerate antipsychotic drugs, because lower doses can be used^[76] and their effects can be rapidly reversed with flumazenil. The therapeutic aims of the drug treatment should be explicit since anxiolytic, sedative and hypnotic effects occur as doses are increased. Benzodiazepines can both protect against delirium and be a risk factor for it; this highlights the need for judicious use in patients dependent on alcohol or benzodiazepines. In addition to this adjunctive use of benzodiazepines, benzodiazepine monotherapy is the treatment of choice when delirium is due to alcohol, benzodiazepine or barbiturate withdrawal or when delirium is due to seizures.^[52,55] Patients suspected of alcohol-withdrawal delirium should receive intravenous thiamine 100 mg/d and folate 1 mg/d; thiamine should precede intravenous glucose. Lorazepam is the preferable benzodiazepine in delirium because of its properties of sedation, rapid onset, short duration of action (thus controllable), lack of major active metabolites and low risk of accumulation.^[1,55]

Emerging therapies

Disturbances of the cholinergic metabolism are implicated in cases in which delirium is caused by hypoxia, traumatic brain injury or hypoglycemia, or is drug related. Anticholinergic delirium is generally treated conservatively by withdrawing the offending agent and occasionally by administering physostigmine.^[15] Other procholinergic agents used to counter cholinergic deficits in dementia have theoretical potential but are not recommended owing to the risk of causing adverse effects. Trazodone and mianserin are antidepressants that share antagonistic actions on serotonin receptors. Open studies of low-dose treatment of delirium with these compounds have found a rapid reduction of noncognitive symptoms in particular. This effect was independent of the mood-altering actions of the

drugs.^[77] Other reports have advocated the use of light therapy,^[78] but the usefulness of this treatment needs to be fully evaluated before it is used routinely.

Conclusion

Clinicians are likely to encounter delirium frequently, particularly in inpatient and intensive care settings. However, it is underrecognized and undertreated because of its heterogeneous and fluctuating presentation. Once manifest, delirium is associated with a worrisome prognosis and higher rates of morbidity and mortality. The cost of health care is on the increase, and more Nigerians are slipping below poverty line. Atypical antipsychotic drugs are expensive, inaccessible and unaffordable in the Nigerian context and have no clear advantage over the typical neuroleptics.

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