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Detection and Management of Pre-Existing Cognitive Impairment and Associated Behavioral Symptoms in the Intensive Care Unit

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Abstract

Recent increase in both the elderly population and associated incidence of dementia are of critical importance to patient care in intensive care units (ICU) in the United States. Identification of pre-existing cognitive impairment such as mild cognitive impairment and dementia could prevent delirium and associated morbidity and mortality in ICU. Additionally, non-cognitive behavioral symptoms such as depression, psychosis, agitation, and catastrophic reactions are common in patients with pre-existing cognitive impairment. Detection and management of non-cognitive behavioral symptoms associated with demented elderly patients in ICU leads to improved delivery of life-saving critical care.

Introduction

The elderly (65+) population, comprised of 36.3 million people, is the fastest growing sector of the United States population (1). The vast majority of the five million elders suffering from dementia in the United States belong to this age group, and the number of dementia cases in the U.S. is expected to triple unless a cure or a preventive strategy is developed (2). This rapid increase in the elderly population and the associated incidence of dementia cases is of critical importance to intensive care units around the country because patients in this age group currently account for 42 to 52% of intensive care unit (ICU) admissions, (3,4) and for more than half of all ICU days (5).

With or without pre-existing cognitive impairments, such as Mild Cognitive Impairment (MCI) or dementia, the application of critical care could provide life-saving benefit to older persons. Pre-existing cognitive impairment does put a patient at heightened risk for complications from intensive care interventions due to their increased vulnerability. For example, patients with dementia have been known to be at the highest risk for developing delirium and subsequent

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poor ICU outcomes (6). While the detection and management of delirium has garnered much interest from critical care specialists, sparse data is available to guide the intensivists in detection and care of patients with dementia in the ICU. The purpose of this paper is to review broadly the available literature on the impact of pre-existing cognitive impairment in care of ICU patients and provide an overview on detection and care of dementia patients for clinicians in the ICU setting.

Definitions of Delirium and Pre-existing cognitive impairment

Delirium is a disorder of sensorium or level of consciousness. Consciousness, defined as a function of the nervous system, is concerned with the perceptual experience of information from the environment and from our own body. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), defines delirium as a syndrome of *disturbed consciousness*, which results in a change in cognition (memory, disorientation, or language disturbance) or in perception from baseline, and is not due to dementia (7).

Dementia is defined as "global decline of cognitive capacity in *clear consciousness*" (8). There are three elements to the definition of dementia. First, the term *global* means that multiple areas of cognition are impaired. Unlike aphasia or amnestic syndrome, dementia means that more than one areas of cognition are impaired. In addition to impairment in memory, other cognitive domains such as language, abstraction, calculation, perception, and judgment are impaired. Second, *decline* means deterioration from previous level of cognitive capacity. This element distinguishes dementia from other cognitive disorders, such as mental retardation and learning disorders, which are present from birth. Additionally, the level of *decline* should be severe enough to impair one's daily activities. This level of decline distinguishes dementia from mild cognitive impairment. Finally, *in clear consciousness* means that the level of consciousness is not impaired. This element distinguishes dementia from delirium. Table 1 lists the DSM IV criteria for the diagnosis of Dementia of the Alzheimer's Type, the most common form of dementia (7).

Most patients with dementia experience measurable cognitive decline before actually meeting the criteria for dementia (9). The clinical entity of *Mild Cognitive Impairment* (MCI) represents the boundary of normal aging and early dementia. It refers generally to complaints of memory functioning in elderly people, which are judged to have a high probability of progressing towards Alzheimer's dementia. The cognitive deficits in a MCI patient are detectable, yet unlike in a patient with dementia, they are not severe enough to impair daily activities (Table 2)(9). It has been estimated that 17 % of the elderly population meet criteria for MCI (10,11), and of those, 10% to 15% progress to dementia every year in comparison to healthy control subjects (12,13). *Pre-existing cognitive impairment* (PCI) is a broader term that refers to either dementia or MCI that is present in chronic form prior to hospital admission (14). This distinguishes PCI from delirium or cognitive impairments that may result directly from the illness or hospitalization.

Pre-existing cognitive impairment and incidence of delirium in ICU

Based on a sample of medical ICU patients above age 65, Pisani et al. reported that prevalence estimates of pre-existing cognitive impairment to be approximately 31% to 37% (14,15). These figures double the prevalence rates of cognitive impairment reported for community dwelling (10-18%) and hospitalized non-ICU (20%) patients with pre-existing cognitive impairment (14). The same study found that patients who have pre-existing cognitive impairments are significantly older, more likely to be women, less likely to be currently married, more likely to have been admitted to the ICU from a nursing home and are more likely to have higher APACHE II scores upon ICU admission (14). However, between patients with and without

pre-existing cognitive impairments, no difference was found between the two groups in terms of characteristics such as education, number of co-morbidities on admission, code status on admission and admission due to respiratory or cardiac causes (14).

Delirium is very common in the ICU with a reported prevalence of nearly 70-87% among patients (16-18). Delirium causes increased morbidity, mortality, nursing home placement, longer ICU and hospital stays, and costlier hospitalizations (19-21). In patients who receive mechanical ventilator assistance, delirium is a predictor of 6-month mortality (22). Patients with one episode of delirium had a 40% increase in length of stay in ICU and total hospital costs, after controlling for confounding variables, compared with patients with no delirium (20).

Several previous studies have demonstrated that dementia is an important risk factor for delirium (23-26). In fact, a recent cohort study of 304 medical ICU patients 60 years of age or older reported that dementia was the strongest risk factor for delirium (odds ratio (OR): 6.3; 95% confidence interval (CR), 2.9-13.8) (18). Other risk factors included the administration of benzodiazepines before ICU admission (OR, 3.4; 95% CI, 1.6-7.0), an elevated creatinine level (OR, 2.1; 95% CI, 1.1-4.0), and low arterial pH (OR, 2.1; 95% CI, 1.1-3.9). Delirium is listed as 1 of the 6 leading causes of preventable injury in those older than 65 years (27), therefore, for patients with pre-existing cognitive impairments, an ICU clinician should be even more vigilant about detection and treatment of delirium in order to reduce the high morbidity and mortality associated with it (22).

Detection of pre-existing cognitive impairment in ICU

Cognitive impairment in medical units is often unrecognized and untreated by hospital physicians (28,29). In a study of 163 medical inpatients in which the prevalence of cognitive impairment was 31%, attending physicians recognized the cognitive impairment in only 13% of cases and junior medical staff recognized it in only 9% of cases (28). Most patients admitted to an acute care hospital do not have prior documentation of their cognitive function (30,31). Since ICU physicians primarily rely on past medical records from referring physicians to obtain information about a patient's baseline cognitive status, pre-existing cognitive impairment may not be appropriately evaluated or managed. In a cohort of 163 acute medical ward patients aged 65 and older, attending physicians were unaware of the existence of previous cognitive impairment in 53% of cases, and intern physicians were unaware in 59% of cases (32).

The biggest barrier to detection of pre-existing cognitive impairment is the fact that direct, in-depth assessment of cognitive functioning is impractical in the ICU setting due to multiple factors, such as mechanical ventilation, related communication difficulties, sedation, wounds, and patient fatigue. Delirium can be diagnosed reliably and rapidly with the Intensive Care Delirium Screening Checklist (33) or the Confusion Assessment Method for the Intensive Care Unit (16; CAM-ICU). Additionally, the Mini-Mental State Examination (MMSE) (34) is a popular, brief cognitive screening tool that can detect severity of global cognitive impairment. However, none of the aforementioned instruments will provide any information about patient's cognitive state before the acute illness. Without information on the previous level of function or cognition, a low score on MMSE could be a reflection of dementia, delirium or delirium superimposed on dementia. Thus, the MMSE by itself will not help differentiate among these three syndromes.

Therefore, the utility of proxy interview- based assessment of pre-existing cognitive impairment has been examined to aid the physicians in ICU. The Modified Blessed Dementia Rating Scale (MBDRS) (35) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (36) were specifically developed for proxy administration and have been widely used for identification of preexisting cognitive impairment in both, outpatient and

hospital settings. Administration of either instrument takes less than five minutes. The MBDRS is an 11-item instrument that has been shown to correlate with pathological assessment of dementia, to discriminate between demented and non-demented subjects, and to correlate well with objective patient measures of dementia. The IQCODE is a 16-item questionnaire designed to measure cognitive decline over time, thus providing a longitudinal perspective of cognitive functioning. The IQCODE has also been shown to correlate with direct patient assessment using cognitive screening tests and has been used to evaluate the presence of dementia in non-critically ill medical inpatients as well as to predict the development of dementia after hospital discharge.

A recent study found that both IQCODE and MBDRS could be reliably used to detect pre-existing cognitive impairment in the ICU (37). The choice of instrument to assess pre-existing CI would depend on the goals of the study. The IQCODE does require a proxy respondent who has observed the patient over a 5-year period. If such proxy is available, IQCODE is more sensitive to detect mild existing cognitive impairment than the MBDRS. In cases in which detection of moderate to severe CI is sufficient and in which proxies with knowledge of the 5-year history of the patients may not be consistently available, the MBDRS is recommended.

Management of Behavioral and Psychological Symptoms of Dementia in ICU

While the most common cause of agitation, psychosis, and mood symptoms in the intensive care setting is delirium, ICU clinicians should be aware of the common behavioral and psychological symptoms of dementia (BPSD). BPSD have become increasingly recognized as part and parcel of the progression of MCI and dementia. Such symptoms include affective disorders (e.g., depression, anxiety, euphoria), personality change, psychotic symptoms (e.g., hallucinations, delusions), and behavioral disturbances (e.g., agitation, aggression, aberrant motor behavior or wandering, apathy, irritability, sleep and eating disturbance, disinhibition).

ICU clinicians are likely to encounter BPSD among patients with pre-exiting cognitive impairment. In the Cardiovascular Healthy Study, among the dementia participants, 75% (n = 270) had exhibited a neuropsychiatric symptom in the past month (62% were clinically significant); 55% (n = 199) reported 2 or more; and 44% (n = 159) 3 or more disturbances in the past month (38). When combined with another study, the 18-month prevalence rate of neuropsychiatric symptoms was estimated to be 88.6% (39). Symptoms appear to be quite persistent as 81% of those who initially had symptoms continued to have symptoms eighteen months later (40).

Prevalence of non-cognitive behavioral symptoms in MCI appears to be also much higher than in general population, but lower than in dementia (38,41). Based on the Memory and Medical Care Study, Chan et al. reported that compared to dementia subjects, those classified as MCI had a lower prevalence (47.1% vs. 66.1%) of any symptoms (psychosis, depression, or agitation), and of agitation (24.8% vs. 45.1%) (40). In the Cardiovascular Health Study, of the 682 individuals with dementia or MCI, 43% of MCI participants exhibited neuropsychiatric symptoms (29% rated as clinically significant) with depression (20%), apathy (15%), and irritability (15%) being most common while 75% of dementia particiapnts exhibited neuropsychiatric symptoms in the previous month (38).

It is important to distinguish behavioral symptoms of delirium from BPSD. Sometimes, depression can closely mimic mild delirium and MCI, and should be in differential diagnosis of all cognitive evaluations. Table 3 compares the features of delirium, dementia, and depression. Behavioral symptoms of delirium are generally associated with acute impairment in the level of consciousness, along with fluctuating level of symptom severity. BPSD tends to be more stable in severity and do not involve impairment in attention. Often, behavioral symptoms of delirium can be superimposed on pre-existing cognitive impairment. In this case,

treatment of underlying cause of delirium should triumph over addressing the behavioral symptoms. The following sections discuss management strategies for specific neuropsychiatric symptoms in the absence of delirium.

A. Depression

Estimates for the prevalence of major depression in patients with dementia are 20% to 25% (42). Depressive disorders in dementia are often somewhat different from those occurring in the absence of dementia. Therefore, overly relying on DSM-IV diagnostic criteria may result in an underdiagnosis and undertreatment of depression among dementia patients in ICU. For example, patients with depression and dementia may not endorse hoplesslenss, suicidal thoughts or worhtlessness. Instead, dementia patients express symptoms such as anxiety, anhedonia, irritablity, lack of motivation and agitation (43). Anxiety is often the most noticeable symptom, and delusions, typically of a paranoid nature, also accompany depression among dementia patients.

Nonpharmacologic or behavioral interventions for the treatment of depression are not practical in the ICU setting. Also, given the presence of cognitive impairment, psychotherapy is generally not beneficial. However, serotonin-specific reuptake inhibitors (SSRI) has been shown to be efficacious in treatment of depression in Alzheimer's disease (AD)(42). It is important to begin at a low dose of SSRI (e.g. about one-fourth of the full adult antidepressant dose, like 25 mg of sertraline) and increase slowly as tolerated, closely monitoring for the development of side effects, as well as improvement in mood. It is also important not to undertreat, recognizing that the majority of patients with AD have optimal responses in the moderate to high dose range (e.g. 100 mg of sertraline) of SSRI. Other non-SSRI options for the treatment of depressive symptoms include starting mirtazapine at 7.5 mg before bedtime, bupriopion at 100 mg once a day of the extended-release preparation, or seronotonin-norepinephrine reuptake inhibitors (e.g. venlafaxine starting at 37.5 mg once a day of the extended release preparation). Table 4 lists common antidepressants and their recommended dosage for treatment of depressive symptoms in patients with mild cognitive impairment or dementia.

B. Delusions and Hallucinations

While delirium is the most common cause of psychotic symptoms in ICU, delusions and hallucinations often occcur in dementia in the absence of delirium. In the absence of clouded sensorium, attentional disturbance, and sleep-wake cycle disruption, psychosis due to dementia should be considered and treated accordingly. Delusions associated with dementia tend to be occur more commonly than hallucinations. In population-based studies, the prevalence of delusions in dementia is approximately 25% while for hallucinations it is 10% to 15% (44). Rather than systemized delusions, dementia patients tend to have isolated paranoid beliefs. For example, when they lose a wallet due to their memory impairment, they might become convinced that it was stolen and persist in this belief despite evidence to the contrary. Among dementia patients, visual hallucinations are also more common than auditory hallucinations, particularly in dementia of Lewy bodies (45). Hallucinations associated with dementia often involve seeing familiar people, including those who are deceased, which may not be distressing to the patients.

Similar to the treatment of depression associated with dementia, behavioral interventions for psychotic symptoms are available, but not practical in ICU setting. Distraction techniques and avoiding arguments are often helpful, but pharmacological interventions might become necessary. Neuroleptices are effective in reducing hallucinations and delusions in dementia patients, but due to safety concerns associated with increased stroke and transient ischemic episode risk in demntia patients, the U.S. Food and Drug Administration added a "black box"

warning for their use in patients with dementia (46). Other side effects to consider include sedation, medication-induced parkinsonism, metabolic syndrome, and orthostatic hypotension, to which the frail elderly patients with dementia are particularly vulnerable to. However, at low doses (e.g. 0.25 – 1 mg of risperidone daily; 2.5 – 5 mg of olzanzapine daily; 12.5 – 50 mg of quetiapine daily), these medications are tolerable and effective in treatment of psychotic sypmtoms in dementia. The decision to initiate neuroleptic treatment involves careful consideration and an open discussion with the patient and family regarding the potential benefits of treatment of hallucinations or delusions versus the potential risk for side effects (47). Close monitoring for reponse and medication side effects is indicated. Table 5 lists common antipsychotics and their recommended dosage for treatment of psychosis in patients with mild cognitive impairment or dementia.

C. Agitation and aggression

Agitated behaviors such as irritablity, yelling, restlessness, and physical aggression are common in dementia with an estimated prevealence of 20 to 25% (44). Clinicians should keep in mind that agitation is a nonspecific phenomenon with a broad differential diagnosis. The most common etiologies for such behaviors include medical illnesses (e.g. UTI, pneumonia), delirium, environmental stressors, psychiatric disorders (e.g., depression psychosis), and the underlying dementia itself. The treament of agitation and aggression will depend on the underlying cause of the behavior (e.g. depression, delirium, pain). If no underlying etiology beside dementia is apparent and the agitation or aggresion is severe, empiric use of neuroleptics can be considered (e.g. 0.25 – 1 mg of risperidone daily; 2.5-5 mg of olanzapine daily; 12.5 – 50 mg of quetiapine daily).

An alternative to atypical antipsychotic agents may be the acetylcholinesterase inhibitors and memantine. Several studies have been shown these agents may help stabilize cognitive as well as behavioral problems in demented patients (45). The reported efficacy among these agents varied, with the greatest positive effects seen with donepezil, which also has the greatest number of studies (48). Other agents such as mood stabilizers such as valproic acid and carbamazepine have been helpful. Anticonvulsants are useful second-line treatments with possible efficacy noted for valproic acid (49,50) and carbamazepine (51).

Also, benzodiazepines can be very effective in maintaining patient and staff safety in a behavioral emergency, but can exacerbate cognitive impairment. Therefore, their use in ICU setting should be kept to a minimum. Lorazepam is a benzodiazepine with the particular advantage of being available for both intravenous and intramuscular use, and a dose of 0.25-0.5 mg is often effective in such emergencies. Midazolam is an ultra-short acting benzodiazepine whose use is usually restricted to critical care settings, which can be similarly useful if intravenous access is available.

Clinicians should keep in mind that one of the most overlooked and undertreated causes of agitation associated with dementia is pain (52). It would be most unfortunate if a dementia patient with agitation from unrecognized pain is given neuroleptic medication that not only fails to address the underlying problem, but can place the patient at risk for side-effects associated with this type of medication.

D. Catastrophic Reactions

A catstrophic reaction is a sudden, out-of-proportion expression of negative emtion (e.g. sadness, frustration, anxiety, anger) that is precipitated by an envirnomental event or an interaction with someone (e.g. family, medical staff) (8). Such reactions often have little warning in a patient who otherwise has appeared calm and content, and they are typically time-

limited. Catastrophic reactions can sometimes be associated with physical aggression. These episodes can be frightening for the patient, as well as for caregivers and staff.

Given that catastrophic reactions are usually time-limited events, reassurance and a calm demeanor by the clinician and staff is generally sufficient. However, in cases of severe episodes, a low dose of an as-needed medication may be helpful during the acute crises. Potential pharmacotherapy interventions include lorazapam (0.25 – 0.5 mg), risperidone (0.25-0.5 mg), quetiapine (12.5 mg to 50 mg), and trazodone (25 – 50 mg). Precipitants for the catastrophic reaction should be identified in order to avoid future recurrence.

E. Other behavioral symptoms

Cognitive impairment is the most common and apparent psychological symptom of dementia. Four cholinesterase inhibitors (i.e., tacrine, donepezil, rivastigmine, and galantamine) are approved for treatment of mild-to-moderate dementia due to Alzheimer's disease. However, given that the benefit of cholinesterase inhibitors or memantine (an NMDA-receptor antagonist agent approved for the treatment of AD) to the long-term progression of dementia has not been shown conclusively, ICU clinicians should not feel compelled to start them during the acute medical management. All cholinesterase inhibitors carry risk of increased gastric acid secretion, nausea, vomiting, and diarrhea. Cholinesterase inhibitors, less commonly, can cause muscle cramps, bradycardia, or exacerbations of asthma. Therefore, it is reasonable to stop cholinesterase inhibitors when dementia patients are admitted to ICU.

Apathy is often mistaken for depression in patients with dementia. Apathetic patients often show diminished volution, low self-motivation, low vitality, diminished emotions, and decreased goal-directed behavior. Unlike depressed patients, apathetic patients usually are not distressed, but appear contented. Psychostimulants (e.g methylphenidate), activating antidepressant agents (e.g., bupropion), and amantadine have been shown benefitial, but in ICU, specific treatment is unlikely to be necessary.

Conclusion

With an aging population and longer life expectancy, the incidence of MCI and dementia is expected to increase in our society. This vulnerable, elderly population with cognitive impairments is likely to be afflicted with medical problems requiring acute hospitalization, often in intensive care units. A substantial proportion of patients with pre-existing cognitive impairments, such as dementia and MCI, are vulnerable to delirium and frequently suffer from non-cognitive, behavioral symptoms. ICU physicians should become vigilant in recognizing pre-existing cognitive impairments to prevent delirium and to aid in the management of neuropsychiatric symptoms associated with dementia. Successful detection and management of non-cognitive, behavioral symptoms associated with dementia in ICU would lead to improved delivery of life-saving critical care to the elderly patients.

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Table 1

DSM IV criteria for the diagnosis of Dementia of the Alzheimer's Type.

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One or more of the following cognitive disturbances:
   - **a.** aphasia (language disturbance)
   - **b.** apraxia (impaired ability to carry out motor activities depite intact motor function
   - **c.** agnosia (failure to recognize or identify objects despite intact sensory function)
   - **d.** disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

1. other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
2. systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
3. substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.

Table 2

Criteria for Amnestic Mild Cognitive Impairment (Petersen et al, 2001)

Memory complaint, preferably corroborated by an informant
Impaired memory function for age and education
Preserved general cognitive function
Intact activities of daily living
Absence of dementia

Table 3

Comparative Features of Delirium, Dementia, and Depression

	Delirium	Dementia	Depression
Definition	Impaired sensorium (reduced level of consciousness)	Global decline in cognitive capacity in clear consciousness	Disturbance in mood, with associated low vital sense and low self-attitude
Core symptoms	Inattention, distractibility, drowsiness, befuddlement	Amnesia, aphasia, agnosia, apraxia, disturbed executive function	Sadness, anhedonia, crying
Common associated symptoms	Cognitive impairment, hallucinations, mood lability	Depression, delusions, hallucinations, irritability	Fatigue, insomnia, anorexia, guilt, self-blame, hopelessness, helplessness
Temporal features	Acute or subacute onset	Chronic onset, usually gradual	Episodic, subacute onset
Diurnal features	Usually worse in the evening and night	No clear pattern	Usually worse in the morning

Table 4

Common antidepressant medications in MCI and Dementia.

Medication	Initial daily dose	Target daily dose	Notable adverse events	Comments
Fluoxetine	10 mg	20-40 mg	Restlessness GI distress Hyponatremia (SIADH)	Long half-life
Sertraline	25 mg	100-150 mg	(same as above)	
Citalopram	10 mg	20-40 mg	(same as above)	Minimal drug-drug interactions
Paroxetine	10 mg	20-40 mg	(same as above) Sedation Anticholinergic effects	
Bupropion	75 mg	150-300 mg	Seizure –rare	Tends to be stimulating
Mirtazapine	7.5 mg	7.5-30 mg	Sedation	Sometimes used as a hypnotic
Trazodone	25 mg	50 mg	Orthostatic hypotension Priapism Sedation	Usually used as a hypnotic
Venlafaxine	37.5 mg	75-150 mg	Restlessness GI distress Hyponatremia (SIADH) Hypertension at high dose	Tends to be stimulating
Duloxetine	20 mg	30-60 mg	Restlessness GI distress Hyponatremia (SIADH)	Also indicated for diabetic neuropathy Likely useful in a variety of comorbid pain syndromes

Table 5

Common antipsychotic medications for patients with MCI or Dementia

Medication	Initial daily dose	Target daily dose	Adverse events	Comments
Risperidone	0.25 mg	0.25-1.0 mg	EPS, elevated prolactin level	Available as orally disintegrating tablet At doses >=6 mg, EPS similar to conventional antipsychotics
Quetiapine	25 mg	25-100 mg	Sedation	Low incidence of EPS
Olanzapine	2.5 mg	2.5-10 mg	Sedation Weight gain Diabetes mellitus	Available in an intramuscular injection and as orally disintegrating tablet
Haloperidol	0.25 mg	0.25-2 mg	EPS Dystonic reactions	Conventional antipsychotic Available as liquid and IM formulations
Fluphenazine	0.25 mg	0.25 – 2mg	EPS Dsytonic reactions	Conventional antipsychotic Available as liquid and IM formulations