Delirium: Where Do We Stand?

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Clinicians are likely to encounter delirium frequently, particularly in inpatient and intensive care settings. However, delirium is underrecognized and undertreated because of its heterogeneous and fluctuating presentation and due to the limitations in resources and training in contemporary clinical settings. Translation of current knowledge about delirium into clinical practice may improve patient care and benefit public health economics. Hence, this review comprehensively discusses the phenomenology and pathophysiology of delirium and its presenting features, risk factors, differential diagnoses, assessment, prognosis, and treatment with antipsychotics; the goal is to facilitate better prevention, recognition, and treatment of delirium. Available research is reviewed, limitations of the research are discussed, and future directions for further delirium research are identified.

Introduction

Delirium is a clinical syndrome characterized by disturbance of consciousness, distractibility, cognitive impairment, and perceptual disturbance [1]; it is secondary to organic insult and often associated with serious and potentially fatal medical or surgical conditions. In a prospective cohort study, delirium has been found to be an independent predictor of higher 6-month mortality and longer hospital stays [2]. A number of studies concur with this finding and also associate delirium with other negative clinical outcomes, such as longer duration of mechanical ventilation, increased rate of nursing home placement, and functional decline [3,4]. Delirium profoundly increases medical expenditures [4]; more than 49% of all hospital days in the United States are spent caring for patients with delirium [5].

Despite the high morbidity, mortality, and economic burden associated with delirium, it remains a poorly understood syndrome. Hence, this review comprehensively discusses the scientific literature related to delirium in the hope that translation from research findings to the clinical setting will assist in improved prevention, detection, and treatment.

How Prevalent Is Delirium, and Which Risk Factors Are Relevant?

Delirium is common among general hospital patients, occurring in 10% to 25% of all acute admissions [6]. However, it increases to 30% to 50% in the hospitalized older adult population, who may be prone to have more complicated and combined medical conditions [6]. In the intensive care unit (ICU), the actual prevalence is reported to reach about 60% to 85%, which may be a low estimate, as delirium frequently presents with hypoactivity that does not alarm staff or caregivers [7]. The difficulty in recognizing delirium is well known, with more than two thirds of cases going unrecognized because of the wide range of symptoms and the disorder's fluctuating nature [6]. In fact, 92% of ICU health care professionals consider delirium to be a significant or very serious problem, yet 78% report that it is underdiagnosed [8].

Risk factors for the development of delirium include hospitalization, advanced age, multiple medical conditions, multiple medications, terminal illness, sensory (hearing or visual) impairment or deprivation, sleep deprivation, dementia, postoperative status, burns, sudden discontinuation of alcohol or drugs, malnourishment, chronic hepatic disease, dialysis, dehydration, Parkinson's disease, HIV infection, and recent stroke [1,6,9]. A recent systematic review reported 25 specific risk factors (21 precipitating and 4 predisposing factors) that influence the onset of delirium in the ICU [10].

Early detection or prevention of delirium may depend on appreciation of such risk factors. In fact, studies have suggested that precipitating and baseline vulnerability factors independently or cumulatively contribute to the development of delirium and that crucial risk factors may successfully validate early prediction of development of delirium (although there are some discrepancies according to research methodology) [11•,12,13]. It has been reported

that three or more delirium risk factors may increase the odds that an individual will suffer from delirium by 60% [13]. In fact, delirium prevention has been demonstrated through modification of some recognized risk factors [6]. Similarly, early detection and active, preventive, multicomponent interventions for delirium have shown economic benefit: active intervention decreased long-term nursing home costs by 15.7% [14].

Are There Proven Etiologic Mechanisms for Delirium?

Delirium is a multifactorial condition with mysterious pathophysiology. It is considered a syndrome of global cerebral dysfunction likely linked to deficits in cerebral metabolism. More specifically, delirium seems to involve specific disturbances in neurotransmitter function and dysregulation of inflammatory agents in the cerebrum [15].

Alterations in neurotransmission underlying delirium include cholinergic, dopaminergic, serotonergic, and γ-aminobutyric acid (GABA) systems. High levels of dopamine activity and low levels of acetylcholine activity may contribute to the development of delirium. In fact, opiates, a common cause of delirium, increase dopamine activity and lower acetylcholine activity [16]. Experimental delirium (and concomitant electroencephalogram [EEG] slowing) also can be produced by anticholinergic drug administration. Higher anticholinergic activity has been found to be correlated with greater severity of cognitive impairment in delirium. GABA-ergic medications also have been associated with both improvement and aggravation of delirium, as have the noradrenergic, glutamatergic, opiatergic, and histaminergic systems [16]. Other neurobiologic factors—such as cytokines, cortisol abnormalities, and oxygen free radicals—are potentially contributory to delirium and thus warrant further study.

Anatomically, the prefrontal cortex and thalamus have been particularly implicated in delirium; these structures are considered the principal regions of behavioral symptoms and cognitive impairment. Cerebrovascular insults in the anteromedial thalamus and posterior parietal cortex present with severe delirium [17]. In depressed patients, caudate lesions may increase delirium incidence. Lesions of the fusiform region can be associated with visual loss and acute, agitated delirium [17].

Discrepancy Between the Perceived Significance and Actual Monitoring of Delirium in Clinical Practice

In a recent nationwide US survey of health care professionals (n = 912), 89% of respondents considered delirium important in the outcome of older adults. However, only 40% reported routinely screening for delirium, and only 16% indicated that they used a specific tool for delirium assessment [8].

A large, retrospective study (n = 267,947) at Veterans Affairs health systems underscores the widespread failure in detecting delirium in clinical practice: the overall rate of recorded delirium and related confusional diagnoses was found to be only 4% [6,18]. This finding demonstrates significant deficits in the detection of delirium in clinical situations in light of prospective studies that report prevalence rates of about 20% to 50% in the hospitalized older adult population [5,19,20].

Several factors have been proposed to explain such underdiagnosis of delirium, including the use of different diagnostic terms (eg, "ICU psychosis"), disguised clinical manifestations of delirium, hypoactive presentation, masking of cognitive changes by pre-existing dementia and psychomotor retarded depression, attribution of symptoms to sensory deprivation from the hospital environment, reduced number of skilled nursing staff, medical staff inexperience, inattentive attitudes toward older adults (ie, hopeless patients), rapid pace and technological focus of contemporary hospital care, and the failure to appreciate the significance of delirium as a marker for severe illness and mortality [18].

Are There Phenomenologic Characteristics of Delirium?

Although the *DSM-IV* clearly defines the criteria for delirium and shows appropriate sensitivity in research settings, detecting delirium in clinical practice is difficult, as the characteristic symptoms are commonly confounded by other neuropsychiatric diseases or medical illnesses. Careful history and physical examination may allow clinicians to distinguish delirium from other disorders. In particular, the onset of the clouding of consciousness, cognitive disturbance, hallucinations, and other symptoms seen in delirium is typically acute and often in the context of obvious medical illness, surgery, or medication change. Delirium may be mistaken for psychotic disorder because auditory and visual hallucinations are common. However, in contrast to delirium, schizophrenia tends to have gradual onset in late adolescence or early adulthood, preceded by a prodromal phase of social isolation that lasts weeks to months. Disorientation and fluctuation of level of consciousness are rare in schizophrenia, but they are hallmark symptoms of delirium. Similarly, onset of the anterograde amnesia and other cognitive dysfunction seen in dementia is typically insidious, with the possible exception of the presentation of a large stroke. Unlike delirium, level of consciousness is generally intact in dementia, and inattention is absent or mild in comparison with other cognitive deficits. Delirium is commonly comorbid with dementia, and this constellation presents further diagnostic issues. Delirium symptoms tend to dominate the clinical picture when the two disorders coexist. Delirium is mistaken for depression at times, particularly when

symptoms are hypoactive in nature. Depression tends to have a more gradual onset of psychomotor slowing, and the cognitive deficits tend to reflect poor effort (they often improve with cues) as opposed to the distractibility or disorientation common in delirium. Adding to the diagnostic complexity, delirious patients present with a wide variety of other psychiatric symptoms, including anxiety, perplexity, language impairment, psychomotor slowing, depressed mood, and irritability. An EEG also can be useful in differentiating delirium from other neuropsychiatric conditions. In patients with delirium, an EEG shows a diffuse slowing of the background, with the exception of patients with delirium tremens, in which the EEG shows fast activity [9]. A quantitative EEG with simple activation procedure (consisting of a 3-minute eyes-open period) is also a clinically useful supplement to the conventional EEG for assessing patients with delirium (the specific activation pattern is absent in delirium patients) [21].

Clinical Course and Outcomes of Delirium

Delirium often follows a waxing and waning course, adding to the difficulty of detection. The phenomenon of "sundowning," which refers to the tendency for delirium symptoms to be worse from late afternoon into the night, has long been reported; this phenomenon has been described to occur in most health care settings [6]. However, "sundowning," which can also occur in patients with dementia in the absence of delirium, should not be considered as a diagnostic indicator.

The duration of delirium has been reported to be approximately 2 weeks. However, a prospective study of patients 65 years old or older admitted to a general medical ward demonstrated that delirium may persist up to 1 year after initial diagnosis [22]. Also, the combined mortality rate over 3.5 years in this sample was approximately 50% [23]. Delirium's negative effects have been consistently demonstrated in many studies [2,7,24,25]; such effects include increase in length of hospital stay, mortality, institutionalization, and medical costs, as well as greater cognitive and functional decline. For example, a prospective cohort study documented a strong association between delirium at discharge and nursing home placement or death over a 1-year follow-up period in general medical patients. In this study, compared with patients who were never delirious, patients with delirium at discharge had a multivariable adjusted hazard ratio of 2.64 for nursing home placement or mortality, whereas patients with resolved delirium had a hazard ratio of 1.53 [25]. Another 1-year follow-up study showed that those who experienced delirium during hospitalization had a 62% increased risk of mortality and lost an average of 13% of 1 year of life compared with patients without delirium [26].

How Can We Improve Detection and Prevention of Delirium? Education and Validated Assessment Tools

Data are mixed regarding the effectiveness of strategies for early detection and prevention of delirium. Systematic detection and multidisciplinary care of delirium have not been shown to be more beneficial than usual care for older patients admitted to medical facilities [27]. Furthermore, data indicate that the consensus guidelines for management of delirium failed to improve the outcomes and process of care in delirium [28]. One promising trial of 852 general medical patients over the age of 70 years that used a preventive intervention consisting of standardized protocols for managing six risk factors for delirium (cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration) significantly reduced the odds of delirium by 40.0%. However, the finding has methodologic limitations and poor generalizability, as the intervention requires a large treatment network and substantial additional medical expenditures [29].

Thus, the importance of developing and using field-applicable management programs to help to prevent delirium has been proposed [3,6]. Cost effectiveness and concise application are relevant considerations given the rapid pace and complexity of contemporary medical settings [6]. In this context, one study using a focused and inexpensive educational program (which consisted of formal presentations to doctors and nurses, written management guidelines, and follow-up sessions) yielded a substantial decrease in delirium prevalence [30]. In several previous studies, a simple educational intervention aimed at health care professionals was consistently found to be effective in early detection and prevention of delirium and in reducing the duration of delirium, length of hospital stay, and mortality [31,32]. Finally, it is important to teach family members about the clinical characteristics and fluctuating course of delirium to improve detection in community settings [3].

Many screening tools are available to aid in identifying delirium in clinical practice, although all have advantages and disadvantages. The Mini-Mental State Examination (MMSE) [33] is widely used by clinicians in general medical settings because of its simplicity and convenience. Other valid, reliable tools include the following: Clock Drawing Test (CDT) [34], Confusion Assessment Method (CAM) [35], Delirium Rating Scale (DRS) [36], Delirium Rating Scale-Revised-98 (DRS-R) [37], Short Portable Mental Status Questionnaire (PMSQ) [38], Delirium Observation Screening Scale (DOS) [39], Memorial Delirium Assessment Scale (MDAS) [40], and Cognitive Capacity Screening Examination (CCSE) [41] in general setting, as well as the NEECHAM Confusion Scale [42], Confusion Assessment Method-ICU (CAM-ICU) [43], Cognitive Test for Delirium (CTD) [44], Abbreviated Cognitive Test for Delirium (ACTD) [45], and Intensive Care Delirium Screening Checklist (ICDSC) [46] in ICU settings.

In addition to differences in the treatment settings in which these scales should be used, the scales have other important differences that should be considered before they are implemented in clinical practice [47]. The CAM [35] and DRS [36] are widely used by nonpsychiatric personnel to diagnose delirium owing to ease of use and extensive validation [47]. It has been suggested that the CAM may be the most useful scale for diagnosing delirium, and the DRS may be best for rating symptom severity and following the course of delirium [48]. However, the DRS item for psychomotor behavior combines hypoactivity and hyperactivity, thereby limiting its usefulness in distinguishing motor subtypes of delirium [36,37]. DRS also lacks items for language impairment, thought process abnormalities, and attention impairment, making it suboptimal for use in observing delirious patients with these particular symptoms [36,37]. The NEECHAM Confusion Scale [42] and the DOS [39] are recommended for screening patients at high risk for delirium, including hospitalized older adults [48]. The NEECHAM Confusion Scale [42] is particularly useful in evaluating for the hypoactive subtype. For ICU patients, the CAM-ICU version is strongly recommended over the CAM [6,43,48]. The MDAS may have a unique role in that it has been validated in cancer patients [48]. A summary of currently available delirium rating scales is presented in Table 1.

Successful application of delirium assessment in clinical practice has the potential to enhance the detection of delirium and reduce the number of delirious patients who go undiagnosed and untreated. Also, as described, some scales are useful for serial monitoring of patients, which may improve the fine-tuning of delirium treatment.

Are There Different Forms of Delirium? Differential Treatment Response and Outcomes

Delirium has been classified according to psychomotor behavior into three subtypes—hyperactive, hypoactive, and mixed—indicating its complex nature. Patients with the hyperactive subtype present with agitation, insomnia, hypervigilance, irritability, distractibility, rapid speech, tangentiality, uncooperativeness, and wandering behavior, making them similar to patients with schizophrenia, bipolar mania, and agitated dementia [49]. Psychomotor slowness, apathy, delayed response, slow speech, and decreased alertness are typical in patients with the hypoactive subtype, who are likely to be confused with patients with depression or dementia [49]. The mixed subtype is characterized by features alternating between the hyperactive and hypoactive subtypes [49].

Health care professionals sometimes assume that the hyperactive subtype is most prevalent in clinical practice, as this subtype comes to attention most easily. However, several studies revealed that the hypoactive subtype is the most prevalent, accounting for more than one half of the delirious patients encountered [4]. One such report by Stagno and colleagues [49] showed the prevalence to be 15% to 80% for hypoactive, 6% to 46% for hyperactive, and 11% to 55% for mixed subtypes. Another study of 122 hospitalized patients determined that delirium was hypoactive in 69% of cases and hyperactive in 29% [50]. This finding has been replicated [3], and another recent replication agreed with these findings [51].

As might be expected, a recent naturalistic study demonstrated that patients with hyperactive delirium tend to be preferentially referred for psychiatric consultation and receive pharmacologic intervention more often than those with the other subtypes [52]. This study also documented improved outcomes in patients referred for psychiatric consultation [52]. This finding importantly demonstrates that delirious patients' presenting symptoms (ie, subtype) influence the likelihood of referral and thus, potentially, clinical outcomes such as treatment response and readmission rate. In fact, anecdotal evidence indicates that the hyperactive subtype may have the best outcome, followed by the hypoactive subtype and then the mixed subtype [49]. There are several other plausible reasons for differential outcomes among delirium subtypes. For example, the hypoactive subtype is more common in older adults, who are prone to having complicated medical conditions [51] such that it may be a marker of a worse medical condition. Data on the course and outcome of the hypoactive subtype may be skewed by including the sickest patients, as milder hypoactive subtypes are frequently undiagnosed or misdiagnosed as depression or dementia [49].

Do We Have Effective and Tolerable Pharmacologic Agents for Treating Delirium? Focusing on Antipsychotics

The treatment of delirium is multifaceted and ideally starts with identifying and correcting the underlying medical cause. Additional components include behavioral modification, environment control, and pharmacologic treatment. Currently available data do not clearly support routine multidisciplinary team interventions for treating delirium because the existing literature reveals methodologic limitations [53,54••].

This section focuses on pharmacologic treatment with antipsychotics, which have been considered the gold standard for treating delirium [8,55]. Antipsychotics have shown consistent efficacy in controlling neuropsychiatric symptoms of delirium and preventing physical exhaustion (avoiding further medical complications) [55]. The American Psychiatric Association practice guidelines [56] and evidence-based guidelines developed by some European countries [57] also recommend using antipsychotics as a crucial treatment modality. It should be reiterated that the primary goal in treating delirium is to identify and correct its underlying cause(s). Hence, comprehensive medical evaluation, including laboratory studies and review of the current medication regimen, is warranted before or simul-

Table 1. Summary of delirium rating scales

Scale	Presence of delirium	Characteristics
Minimal training		
Mini-Mental State Examination [33]	≤ 20	5 domains/30 points; 10–20 min; widely used by most clinicians; requires verbal communication from patient; not proper to use in ICU setting
Cognitive Capacity Screening Examination [41]	≤ 19	7 domains/31 points; quick differentiation between the "functional psychoses" and diffuse organic brain syndromes; 10–20 min
Short Portable Mental Status Questionnaire [38]	≥ 3	10 items/10 points; possible errors for diagnosis of delirium
Clock Drawing Test [34]	Depending on completion	Focuses on psychomotor skill tests; also useful for Alzheimer's disease
High training		
Memorial Delirium Assessment Scale [40]	≥ 7	10 items/30 points; especially useful for repeated assessments, severity; does not include items for diagnosis
Confusion Assessment Method [35]	Positive = presence of items 1 and 2 and either 3 or 4	9 items; best diagnostic tool; no rating of severity; not proper to use in ICU setting; 20 min
Confusion Assessment Method-ICU [43]	Positive = presence of features 1 and 2 and either 3 or 4	4 features only; very quick (2–3 min); useful for ICU setting
Delirium Rating Scale [36]	≥ 12	10 items/32 points; useful in screening diagnosis and symptom severity; widely validated and available in many different languages
Delirium Rating Scale-Revised-98 [37]	≥ 15	16 items/46 points; 13 severity items and 3 diagnostic items; ideal for longitudinal studies
NEECHAM Confusion Scale [42]	≤ 24	3 subscales/9 items/54 points; particularly useful at delirium's onset and in patients with "quiet" manifestations; useful in ICU setting; 5 min
Cognitive Test for Delirium [44]	≤ 22	5 domains/30 points; developed for ICU setting; 100% sensitivity; 10–15 min
Abbreviated Cognitive Test for Delirium [45]	≤ 10	Visual attention span and recognition memory for pictures only; 28 points; more practical for use by ICU clinicians
Intensive Care Delirium Screening Checklist [46]	≥ 4	8 items/8 points; useful for ICU setting; especially for patients with language disturbance
Delirium Observation Screening Scale [39]	≥ 3	25 items; developed for proper use by nurse

ICU—intensive care unit.

taneous with the initiation of pharmacologic treatments. In this regard, there are delirium etiologies in which antipsychotic agents would not be first-line treatment; alcohol or sedative withdrawal is a chief example, and benzodiazepines have become the standard of care.

Many antipsychotic agents are currently available. Haloperidol remains the most-studied agent to date. In principle, the choice of antipsychotic for delirium should be based on the presenting symptoms (ie, hyperactive vs hypoactive subtype); the underlying etiology of the delirium; and any associated comorbid medical conditions, which sometimes represent contraindications to specific agents. Hyperactive delirium may deserve more sedating antipsychotics than hypoactive delirium. Prior evidence of QTc prolongation in the electrocardiogram warrants using agents with less conduction effects (or more intensive monitoring via telemetry). It has also been proposed that post-traumatic brain injury delirium be treated with atypical antipsychotics, which are less-specific dopamine 2–receptor antagonists, because of observations that haloperidol slows cognitive recovery [58]. Data are limited to suggest superiority of one agent over another in the treatment of delirium in general.

Haloperidol has been the most frequently used antipsychotic medication in the treatment of delirium for several decades [6]. Atypical antipsychotic agents have become first-line in the treatment of schizophrenia because of their lower incidence of extrapyramidal symptoms and tardive dyskinesia. The risks of extrapyramidal symptoms with haloperidol are generally believed to be markedly reduced with parenteral as opposed to oral administration. However, multiple case reports link intravenously administered haloperidol to QTc prolongation, prompting recommendations that patients treated in this fashion should have electrocardiogram monitoring; steps to be taken may include telemetry, cardiac consultation, and dose reduction or discontinuation [58]. Previously, intravenous droperidol was commonly used to treat delirium, but this agent has fallen out of favor because of similar cardiac effects and risks of severe hypotension. Parenteral administration of treatment for delirium has obvious advantage in agitated and uncooperative patients. At this time, intramuscular forms of atypical antipsychotics are available, including ziprasidone, olanzapine, and aripiprazole. Other options include rapidly dissolving oral forms of olanzapine, aripiprazole, and risperidone, which are pharmacokinetically similar to the traditional oral forms but eliminate the need for swallowing.

Table 2 summarizes currently available trials of antipsychotics for treating delirium. As noted, randomized, double-blind, placebo-controlled trials of antipsychotics in the treatment of delirium are lacking.

Finally, a meta-analysis of 17 placebo-controlled trials of atypical antipsychotics in the older adult population revealed an increased risk of death in the drug-treated patients by 1.6 to 1.7 times compared with that seen in placebo-treated patients [59]. Mortality was largely considered to be related to cardiovascular effects and risk of aspiration pneumonia. The US Food and Drug Administration has subsequently issued a black box warning in atypical antipsychotics' labeling that describes this risk. The US Food and Drug Administration is considering a similar warning for the labeling of typical antipsychotics [59]. Thus, clinicians need to use judgment when prescribing antipsychotics for delirium, as the preponderance of patients with delirium are older adults or are medically compromised. It seems prudent to minimize the dose and duration of antipsychotic treatment of delirium because of the risks described. It has been suggested that antipsychotic use be low-dose and short-term (eg, haloperidol, 1–2 mg orally every 4 hours as needed or 0.25–0.50 mg orally every 4 hours for older adults) [54••]. No controlled studies have identified the adequate duration of antipsychotic use in delirium, but antipsychotics may be maintained until 7 to 10 days after resolution of delirium; normalization of the sleep/wake cycle is often the last symptom of delirium to resolve.

Conclusions

Delirium is a complex neuropsychiatric syndrome presenting primarily with disturbances of cognition, perception and sensorium, alertness, sleep/wake cycle, and psychomotor behavior in the context of a medical etiology. As described, the presentation can be quite variable among patients and even within a given patient because of the notorious waxing and waning course. This variability and overlap with other psychiatric syndromes has led to substantial underrecognition and undertreatment in clinical settings. Considering the significant morbidity and mortality associated with delirium and the tremendous economic burden, the rampant failure to diagnose, refer, and treat such patients represents a critically important public health care issue. Clinicians should be systematically educated about delirium symptoms. Also, caregivers and family members of medically compromised patients should be educated about recognizing delirium. The use of structured diagnostic instruments and scales to follow the severity of symptoms has been an improvement in the field. However, much more research is needed into the use of such instruments and how they can be applied to clinical situations to improve the detection and treatment of delirium. Similarly, research is warranted that focuses on preventing delirium, potentially by identifying susceptible patients and intervening early. It is particularly challenging to devise cost-effective intervention for preventing and identifying delirium early in its course given the rapid pace and limitations in resources in inpatient and ICU settings. Furthermore, data to date do not clearly indicate that such systems have proven benefit. Still, the indisputable health and financial costs of delirium indicate that this should be a high priority.

There is also a general lack of research on effective treatments for delirium, particularly regarding the use of newer atypical antipsychotics. The field currently relies on small studies and case reports to formulate conclusions about the efficacy and tolerability of antipsychotics for delirium. Large, comparative studies of atypical antipsychotics would greatly enhance our application of appropriate treatment of delirium in clinical settings.

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Table 2. Summary of recent clinical trials and case studies of antipsychotics for delirium

Antipsychotics	Number of patients	Assessment	Response*	Dosage (mean, *mg/d*)	Days of improvement (mean, *d*)
Olanzapine† [60]	79	MDAS	46*	6.3‡	No data available
Olanzapine† [61]	20	DRS	54*	5.9	3.8
Risperidone† [62]	10	DRS	47*	1.7§	7.1
Risperidone† [63]	10	DRS	55*	0.75‡	3.9
Risperidone† [64]	64	DRS	70*	2.6‡	No data available
Quetiapine† [65]	11	DRS	87.1*	211.4	3
Quetiapine† [66]	12	DRS	56*	93.8‡	5.9
Quetiapine† [67]	12	DRS	49*	44.9	4.8
Quetiapine† [68]	22	DRS-R-98	57*	127.1	7.1
Aripiprazole†¶ [69]	No data available	MMSE/DRS	43/34**	22.5	4.5
Aripiprazole† [70]	14	DRS-R-98	62.5	8.9	6.7††
Ziprasidone† [71]	1	DRS	12**	100	No data available
Ziprasidone (IV)† [72]	1	NA	NA	20	5 min after IV
Amisulpride vs quetiapine‡‡ [73]	16 vs 15	DRS-R-98	66.7 vs 65.3	156.4 vs 113	6.3 vs 7.4
Perospirone† [74]	38	DRS-R-98	70.7	6.5§/10§§	5.1
Haloperidol† [75]	10	DRS	54*	5.4	6
Haloperidol vs risperidone¶¶ [76]	12 vs 12	MDAS	No data available	1.7 vs 1.0	4.2 vs 4.2
Haloperidol vs risperidone† [77]	24 vs 18	DRS-R-98	63 vs 55*	1.7 vs 1.2	6.7 vs 4.8
Haloperidol vs olanzapine† [78]	45 vs 28	DI	No data available	4.5 vs 6.5	No data available
Haloperidol vs olanzapine vs placebo*** [79]	72 vs 74 vs 29	DRS	70.4 vs 72.2 vs 29.7	7.1 vs 4.5 vs placebo	3.4 vs 2.8 vs 5.2
Haloperidol vs placebo††† [80]	212 vs 218	Incidence of postoperative delirium	15.1 vs 16.5	1.5 vs placebo	NA

*Mean percentage reduction in primary outcome.
†Open-label study or case report.
‡Dosage at end of study.
§Mean maximal daily dose.
¶Analysis of 2 cases.
**Exact or mean difference in primary outcome.
††Mean peak response.
‡‡Randomized, open-label study.
§§Mean initial dosage.
¶¶Randomized, double-blind study.
***Randomized, placebo-controlled study.
†††Randomized, double-blind, placebo-controlled study.
DI—Delirium Index; DRS—Delirium Rating Scale; DRS-R-98—Delirium Rating Scale-Revised-98; IV—intravenous; MDAS—Memorial Delirium Assessment Scale; MMSE—Mini-Mental Status Examination; NA—not applicable.

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