Trial Results

Table S1: Antipsychotic treatment trials for the prevention of delirium (reference numbers refer to references listed at the end of this document).

RD=Risk Model for Delirium (66), DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed (71), IV=intravenous, NS=normal saline, ICU=intensive care unit, CAM-ICU=Confusion Assessment Method for The ICU (72), LOS=length of stay, DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (73), DRS-R–98=Delirium Rating Scale-Revised–98 (74), CAM=Confusion Assessment Method (75), ICDSC=Intensive Care Delirium Screening Checklist (76).

Note: All reported differences were statistically significant, unless stated otherwise.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Vochteloo et al. 2011 (66)	Hip fracture patients with a high risk for developing delirium were treated with prophylactic haloperidol 1 mg twice daily and a group of geriatric hip fracture patients with a low risk for developing delirium received no treatment.	Two groups of geriatric hip fracture patients (age>65): 1) At high risk for developing delirium (RD score≥5), and 2) at low risk for developing delirium (RD score<5). Prevalence rates of delirium at baseline not reported.	Haloperidol (N) = 205 No Treatment (N) = 173	Non-random assignment, open label, parallel two arm, no treatment comparator trial. Fixed dosing regimen.	Many	DSM-IV	RD	Not reported	Not reported	Larger proportion of high risk subjects receiving haloperidol diagnosed with delirium during hospitalization compared to low risk subjects receiving no treatment (42.4% versus 14.1%), p<.001	1. Higher proportion of high-risk patients treated with haloperidol had a hospital length of stay ≥ 10 days compared to the low risk patients without treatment (65.1% vs. 44.1%), p<.001. 2. Higher 12 month mortality rates for the high risk patients treated with haloperidol compared to the low risk patients without treatment (37% vs. 14.6%), p<.001.
Wang et al. 2012 (5)	ICU patients received either an initial haloperidol 0.5 mg IV bolus or NS following non-cardiac surgery, followed by a continuous infusion of IV haloperidol 0.1 mg/hr or placebo for 12 hours. Both treatment groups received Inouye's multi-component treatment interventions.	Geriatric patients (age>65) admitted to an ICU after non-cardiac surgery. Prevalence rates of delirium at baseline not reported.	Haloperidol (N) = 229 Placebo (N) = 228	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	1. Duration of surgery was significantly longer for the haloperidol treated subjects. 2. Total intra-operative IV infusion volume was greater for the haloperidol treated subjects compared to the placebo group.	CAM-ICU	No risk prediction model used.	Not reported	Not reported	Smaller proportion of haloperidol treated subjects diagnosed with post-operative delirium compared to placebo treatment (15.3% vs. 23.2%), p<.05.	1. Shorter ICU LOS for haloperidol treated subjects compared to the placebo group (median hours: 21.3 vs. 23), p=.024. 2. No differences in total hospital LOS. 3. No differences in 28 day all cause mortality.
Prakanrattana et al. 2007 (8)	ICU patients received a single dose of oral risperidone 1 mg or placebo following elective cardiac surgery.	Geriatric patients (mean age=61) who underwent elective cardiac surgery and admitted post-operatively to the ICU. Patients experiencing pre-operative delirium were excluded.	Risperidone (N) = 63 Placebo (N) = 63	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	None reported	CAM-ICU	No risk prediction model used.	Not reported	Not reported	Lower incidence of post-operative delirium in the risperidone treatment group vs. placebo treatment (11.1% vs. 31.7%), p<.01.	1. No differences in ICU LOS. 2. No differences in total hospital LOS.
Larsen et al. 2010 (10)	Patients received one 5 mg dose of olanzapine or placebo prior to elective total knee- or total hip-replacement surgery and a repeat 5 mg dose of olanzapine or placebo post-operatively.	Geriatric patients (age≥65) scheduled for elective total knee- or total hip-replacement surgery. Prevalence rates of delirium at baseline not reported.	Olanzapine (N) = 196 Placebo (N) = 204	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	1. Greater proportion of placebo treated subjects undergoing complex joint surgery (i.e. bilateral joint-replacement or joint-revision surgery) compared to the olanzapine group. 2. Greater proportion of placebo treated subjects had an ASA score of 3 compared to olanzapine treated subjects.	DSM-III-R	No risk prediction model used.	Not reported	DRS-R-98	1. Smaller proportion of olanzapine treated subjects diagnosed with post-operative delirium compared to placebo treatment (14.3% vs. 40.2%), p<.0001. 2. Duration of delirium episodes longer for olanzapine treated subjects compared to the placebo group (mean days: 2.2 vs.1.6), p<.05. 3. Severity of delirium symptoms greater for olanzapine treated subjects compared to the placebo treatment (expressed as max DRS-R-98 score on the first day of delirium: 16.44 vs. 14.5), p<0.05.	Larger proportion of olanzapine treated subjects discharged to home with services compared to the placebo group (40.8% vs. 29.9%), p=.02.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Kaneko et al. 1999 (6)	ICU patients who underwent elective gastrointestinal surgery received post-operatively, either haloperidol 5 mg IV or NS daily for 5 days.	Geriatric ICU patients (mean age=72.8) who underwent elective gastrointestinal surgery. Prevalence rates of delirium at baseline not reported.	Haloperidol (N) = 40 Placebo (N) = 40	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	None reported	Not reported	No risk prediction model used.	Not reported	Not reported	1. Smaller proportion of haloperidol treated subjects diagnosed with post-operative delirium compared to placebo treatment (10.5% vs. 32.5%), p< .05. 2. Duration of delirium episodes shorter in haloperidol treated subjects compared to the placebo group (data and p-value not reported). 3. Severity of delirium symptoms lesser in haloperidol treated subjects compared to the placebo group (data and p-value not reported).	Not reported
Kalisvaart et al. 2005 (7)	Patients undergoing acute or elective hip surgery at intermediate or high risk for post-operative delirium received oral haloperidol 0.5 mg three times daily or placebo started on admission (permitted maximum delay to surgery = 72 hours), and continued for three days post-operatively.	Geriatric patients (age>70) admitted for acute or elective hip surgery at intermediate or high risk for post-operative delirium. Patients with baseline delirium excluded.	Haloperidol (N) = 212 Placebo (N) = 218	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	None reported	DSM-IV and CAM	Inouye predictive model for delirium (1993;1996).	Not reported	DRS-R-98	1. No difference in incidence of post-operative delirium between haloperidol and placebo treated groups. 2. Duration of delirium episodes shorter in the haloperidol treated group compared to the placebo group (mean days: 5.4 vs. 11.8), p<.001. 3. Severity of delirium symptoms lesser in the haloperidol treated group compared to placebo treatment (expressed as highest DRS-R-98 score:14.40 vs.18.41), p<.001.	Total hospital LOS shorter for haloperidol treated subjects compared to the placebo treatment (mean days:17.1 vs. 22.6), p<.001
Hakim et al. 2012 (9)	ICU patients with subsyndromal delirium received 0.5 mg oral risperidone or placebo every 12 hours following on pump cardiac surgery and continuing for 24 hours after resolution of subsyndromal delirium or a diagnosis of "possibly delirious" was achieved.	Geriatric (age>65) ICU patients with subsyndromal delirium (ICDSC score of 1–3) following on pump cardiac surgery. Patients with baseline delirium excluded.	Risperidone (N) = 51 Placebo (N) = 50	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	None reported	ICDSC>3 and DSM-IV	No formal risk prediction model used. However, all subjects at elevated risk for delirium by carrying a diagnosis of Subsyndromal delirium (ICDSC score=1-3).	Not reported	ICDSC	1. Lower incidence of post-operative delirium in the risperidone treated group compared to placebo treatment (13.7% vs. 34%), p<.05. 2. No differences in duration of delirium episodes. 3. No differences in severity of delirium symptoms.	1. No differences in ICU LOS. 2. No differences in total hospital LOS.

Table S2: Antipsychotic trials for the treatment of acute delirium (reference numbers refer to references listed at the end of this document).

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed (71), IV=intravenous, ICU=intensive care unit, CAM-ICU=Confusion Assessment Method for The ICU (72), LOS=length of stay, DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (73), DRS-R–98=Delirium Rating Scale-Revised–98 (74), CAM=Confusion Assessment Method (75), ICDSC=Intensive Care Delirium Screening Checklist (76), KPS=Karnofsky Performance Scale (77), DSM-IV-TR=Diagnostic and statistical manual of mental disorders, 4th ed., text rev (78), DRS=Delirium Rating Scale (79), AIDS=Acquired Immunodeficiency Syndrome, NA=not applicable, MDAS=Memorial Delirium Assessment Scale (80), DI=Delirium Index (81), DRS-J=Delirium Rating Scale, Japanese Version (82).

Note: All reported differences were statistically significant, unless stated otherwise.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Girard et al. 2010 (11)	Mechanically ventilated ICU patients "with an abnormal level of consciousness" received a starting dose of either: haloperidol 5 mg, ziprasidone 40 mg, or placebo via gastric access or IM every 6 hours with flexible dosing based on clinical judgment. Study drug was discontinued when subjects were delirium or coma free for 48 hours or treated to a maximum of 14 days.	Middle aged (median=53.7) mechanically ventilated medical and surgical ICU patients with "an abnormal level of consciousness or were receiving sedative or analgesic medications". 47.5 % of subjects were delirious at baseline, 34.6% of subjects were comatose at baseline.	Haloperidol (N) = 35 Ziprasidone (N) = 30 Placebo (N) = 36	Randomized, double blind, placebo controlled, parallel three arm trial. Flexible dosing regimen.	No	CAM-ICU	Not reported	Not reported	1. No differences in proportion of subjects experiencing resolution of delirium between haloperidol, ziprasidone and placebo treatment groups (69% vs. 77% vs. 58%), p=0.28. 2. No differences in duration of delirium episodes.	1. No differences in ICU LOS. 2. No differences in total hospital LOS. 3. No differences in hospital mortality rates. 4. No differences in time on ventilatory support.
Devlin et al. 2010 (16)	Delirious ICU patients received a starting dose of quetiapine 50 mg or placebo enterally every 12 hours. Subsequent dosing was flexible to a maximum of 200 mg of quetiapine every 12 hrs based on subject's clinical status. Study drug was continued until subjects were delirium free, they were discharge from the ICU or to a maximum of 10 days of treatment.	Geriatric (mean age=63) delirious (ICDSC>4) medical and surgical ICU patients.	Quetiapine (N) = 18 Placebo (N) =18	Randomized, double-blind, placebo controlled, parallel two arm trial. Flexible dosing regimen.	1. Prior to ICU admission 67% of quetiapine treated subjects and 50% placebo treated subjects came from home. 2. 24 hours prior to randomization mean Fentanyl dose received by the quetiapine treated group = 0 μg and by the placebo treated group = 520 μg.	ICDSC≥4	When an ICDSC score≤3 was first detected.	ICSDSC	1. During the period of study drug administration delirium resolved at least once in 100% of quetiapine treated compared to 78% of placebo treated subjects (p=.05). 2. No differences in proportion of subjects with delirium recurrence. 3. Median time in state of delirium shorter in the quetiapine treated compared to placebo group (36 hrs versus 120 hrs), p=.006.	1. No differences in ICU LOS. 2. No differences in total hospital LOS. 3. No differences in hospital mortality rates. 4. Trend level greater proportion of quetiapine treated subjects discharged home or to a rehabilitation center compared to the placebo group (89% vs. 56%), p=.06.
Tahir et al. 2010 (40)	Delirious patients received oral quetiapine 25 mg once daily or placebo with dose titration to a maximum daily dose of 175 mg of quetiapine or placebo in divided doses based on subjects' clinical status until resolution of delirium or a maximum of 10 days treatment.	Geriatric (mean age=84.2) delirious general medical, surgical and orthopedic patients.	Quetiapine (N) = 21 Placebo (N) = 21	Randomized, double blind, placebo controlled, parallel two arm trial. Flexible dosing regimen.	No	DSM-IV and DRS-R-98>15	DRS-R-98 total score<15	DRS-R-98	1. No differences in proportion of subjects experiencing resolution of delirium between quetiapine and placebo treatment groups. 2. Trend level more rapid rate of decrease of DRS-R-98 total score for quetiapine treated subjects compared to placebo treatment (Rate diff=0.55, p=.05).	Not reported
Boettger et al. 2011 (12)	Delirious cancer patients treated with either aripiprazole or haloperidol with a flexible dosing regimen on the basis of subjects' clinical status.	Geriatric (mean age=66.8) delirious cancer patients referred to psychiatry service for treatment of delirium.	Aripiprazole (N) = 21 Haloperidol (N) = 21	Non-random assignment, open label, parallel two arm, active comparator trial. Flexible dosing regimen.	The mean KPS score at baseline was significantly higher in aripiprazole treated subjects (28.1) compared to the haloperidol group (22.4).	DSM-IV-TR	MDAS<10	MDAS	1. Similar proportions of aripiprazole vs. haloperidol treated groups experienced delirium resolution over 4-7 days (76.2% vs. 76.2%). 2. Delirium severity decreased significantly and similarly for aripiprazole vs. haloperidol (Mean MDAS decrease: 9.8 vs 13.1) diff p=ns.	Not reported

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Grover et al. 2011 (41)	Delirious general hospital patients received flexible dosing (based on clinician judgment) of either: haloperidol, risperidone or olanzapine. Duration of treatment dependent upon clinician judgment.	Middle aged (mean age=45.3) hospitalized delirious patients referred to the Psychiatry Consultation service for treatment of delirium.	Haloperidol (N) = 20 Risperidone (N) = 21 Olanzapine (N) = 23	Randomized, single blind, parallel three arm, active comparators trial. Flexible dosing regimen.	Mean duration of delirium prior to enrollment; haloperidol (41.71 hours), olanzapine (64 hours), risperidone (77.2 hours).	DRS-R-98 and CAM	Not reported	DRS-R-98	Delirium severity decreased significantly and similarly for haloperidol, risperidone and olanzapine treatment groups (mean DRS-R-98 decrease from day 0-6: 15.33 vs. 15.47 vs. 11.05, diff p=ns.	Not reported
Skrobik et al. 2004 (13)	Delirious ICU patients received a flexible dosing regimen (based on clinician judgment) of either olanzapine (mean=4.5 mg/day) or haloperidol (mean=6.5 mg/day).	Geriatric (mean age=64.9) delirious patients in a medical-surgical ICU.	Haloperidol (N) = 45 Olanzapine (N) = 28	Randomized, single blind, parallel two arm, active comparators trial. Flexible dosing regimen.	1. Trend towards olanzapine treated patients being older (mean age=67.5) than haloperidol treated patients (mean age=63.2). 2. Trend towards more surgical urgent admissions for the haloperidol treated group (37.8) compared to the olanzapine treated group (14.2%).	ICDSC≥4 and DSM-IV	Not reported	DI	Delirium severity decreased significantly and similarly for haloperidol and olanzapine treatment groups (DI change score day 1-5: data not available, diff p=ns).	Amount of IV rescue haloperidol used was equivalent between haloperidol and olanzapine treatment groups.
Han et al. 2004 (42)	Delirious general hospital patients received flexible dosing haloperidol (mean= 1.71 mg/day) or risperidone (mean=1.02 mg/day) for 7 days.	Geriatric (mean age = 66) delirious general hospital patients referred to the Psychiatry consultation service.	Haloperidol (N) = 12 Risperidone (N) = 12	Randomized, double blind, parallel two arm, active comparator trial. Flexible dosing regimen.	No	DSM-III-R	MDAS<13	MDAS	1. Non-significantly greater proportion haloperidol compared to risperidone treated subjects experiencing delirium resolution (75% vs 42%, p=.11) 2. No differences in duration of delirium episodes. 3. Delirium severity decreased significantly and similarly for haloperidol and risperidone treated subjects (MDAS change score: data not available, diff p=.14)	Not reported
Sipahimalani et al. 1998 (14)	Delirious general hospital patients received a flexible dosing regimen of either olanzapine (range=5mg to 15 mg at bed time) or haloperidol (1.5 mg to 10 mg/day).	Geriatric (mean age=64) delirious general hospital patients referred to the Psychiatry Consultation service.	Haloperidol (N) = 11 Olanzapine (N) = 11	Non-random assignment, open label, parallel two arm, active comparator trial. Flexible dosing regimen.	No	Not reported	Not reported	DRS	Delirium severity decreased significantly and similarly for haloperidol and olanzapine treatment groups (Defined by >50% decrease in DRS scores: 54.5% vs. 45.4%), p-not provided.	Not reported
Lee et al. 2005 (43)	Delirious hospitalized patients received a flexible dosing regimen (based on clinician judgment) of either amisulpride (mean=156.4 mg/day) or quetiapine (mean=113 mg/day).	Geriatric delirious patients (mean age=61.9) from Neurosurgery, Orthopedic Surgery, Internal Medicine, Neurology and Rehabilitation Medicine services referred to the Psychiatry consultation service.	Quetiapine (N) = 15 Amisulpride (N) = 16	Randomized, open label, parallel two arm, active comparator trial. Flexible dosing regimen.	No	DSM-IV	Not reported	DRS-R-98	Delirium severity decreased significantly and similarly for quetiapine and amisulpride treatment groups (Average DRS-R-98 reduction: 6.6 vs. vs. 7), p=0.84.	Not reported
Kim et al. 2010 (15)	Delirious general hospital patients received a flexible dosing regimen (based on clinician judgment) of either risperidone (mean=0.9 mg/day) or olanzapine (mean=2.4 mg/day) for 7 days.	Geriatric (mean age=70) delirious general hospital patients.	Risperidone (N) = 17 Olanzapine (N) = 15	Randomized, single blind, parallel two arm, active comparator trial. Flexible dosing regimen.	No	DSM-IV	DRS-R-98 score reduction≥50% from baseline.	DRS-R-98	1. Time to response not significantly different between risperidone and olanzapine (Median days: 5 vs. 3), p=0.29. 2. Delirium severity decreased significantly and similarly for both treatment groups (reduction in DRS-R-98 score: data not provided), diff p=ns.	Not reported

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Platt et al. 1994 (65)	Delirious hospitalized AIDS patients received a flexible dosing regimen of either chlorpromazine or haloperidol, dosing based on DRS scores.	Adult (age not reported) delirious hospitalized AIDS patients.	Chlorpromazine (N) = 10 Haloperidol (N) = 10	Randomization and blinding not reported. Parallel two arm, active comparator trial. Flexible dosing regimen.	Not reported	DSM-III-R and DRS>12	Not reported	DRS	"…chlorpromazine, even though sedating and anticholinergic, was at least as effective as haloperidol." Neither data nor p-value reported for this comparison.	Not reported
Breitbart et al. 1996 (44)	Delirious hospitalized AIDS patients treated with flexible dosing haloperidol, chlorpromazine or lorazepam to achieve DRS<13 or not hallucinating. Mean maintenance daily doses (Day 2 – end) below: 1. Haloperidol: 1.4 mg 2. Chlorpromazine: 36 mg 3. Lorazepam: 4.6 mg	Adult (mean age=39.2) hospitalized AIDS patients who developed incident delirium following admission.	Haloperidol (N)=11 Chlorpromazine (N) =13 Lorazepam (N) = 6	Randomized, double blind, parallel three arm, active comparator trial. Flexible dosing regimen.	Not reported	DRS≥13 DSM-III-R	DRS<13	DRS	1. DRS scores decreased significantly and no differently for haloperidol compared to chlorpromazine (Mean DRS score reduction, baseline to end: (8.81 vs. 8.87) 2. Both haloperidol and chlorpromazine superior to lorazepam in DRS score reduction: Mean lorazepam DRS reduction=1.33. 3. All lorazepam treated subjects developed treatment limiting side effects necessitating early discontinuation: over-sedation, disinhibition, ataxia, increased confusion.	Not Reported
Breitbart et al. 2002 (19)	Delirious hospitalized cancer patients received a flexible dosing regimen of olanzapine (mean=3 mg/day).	Geriatric (mean age=60.6) delirious cancer patients referred to the psychiatry service	Olanzapine (N) = 76	Open label, single arm trial. Flexible dosing regimen.	NA	DSM-IV	MDAS≤10	MDAS	More than 75% of olanzapine treated subjects achieved delirium resolution, p= .001	Not reported
Kishi et al. 2012 (67)	Delirious hospitalized cancer patients received a flexible dosing regimen (based on clinician judgment) of risperidone (mean=1.4 mg/day) for 7 days.	Geriatric (mean age=68.9) delirious cancer patients referred to the psychiatric consultation service.	Risperidone (N) = 29	Open label, single arm trial. Flexible dosing regimen.	NA	DSM-IV-TR	DRS-R-98 severity scale score≤10	DRS-R-98	37.9% of risperidone treated subjects achieved remission of delirium within 7 days, p=.01.	Not reported
Sasaki et al. 2003 (68)	Delirious patients received a flexible dosing regimen (based on clinician judgment) of quetiapine(mean=44.9 mg/day).	Geriatric (mean age=67.3) delirious general hospital patients	Quetiapine (N) = 12	Open label, single arm trial. Flexible dosing regimen.	NA	DSM-IV	DRS-J total score<12	DRS-J	Mean duration of quetiapine treatment until remission of delirium = 4.8 days.	Not reported
Pae et al. 2004 (17)	Delirious hospitalized patients received a flexible dosing regimen (based on clinician judgment) of quetiapine (mean=127 mg/day).	Geriatric (mean age=69.1) delirious patients from neurosurgery, orthopedic surgery and oncology departments	Quetiapine (N) = 22	Open label, single arm trial. Flexible dosing regimen.	NA	DSM-IV	DRS-R-98 severity score<15	DRS-R-98	1. 86.3% of quetiapine treated subjects achieved delirium resolution. 2. DRS-R-98 scores decreased from 21.8 pre-treatment to 9.3 post-treatment, p< .0001.	Not reported
Kim et al. 2003 (18)	Delirious acute medical patients received a flexible dosing regimen (based on clinician judgment) of quetiapine (mean= 93.75 mg/day).	Geriatric (mean age=74) delirious acute medical patients	Quetiapine (N) = 12	Open label, single arm trial. Flexible dosing regimen.	NA	DSM-IV	Not reported	DRS	Delirium severity decreased significantly over an average 5.9 day follow-up period (Mean DRS score change: 18.25 to 0.63	Not reported
Parellada et al. 2004 (69)	Delirious acute medical patients received flexible dosing (According to clinician judgment) oral risperidone (mean=2.6 mg/day).	Geriatric (mean age=67.3) delirious acute medical patients	Risperidone (N) = 64	Open label, single arm trial. Flexible dosing regimen.	NA	DSM-IV	DRS total score<13	DRS	1. 90.6% of risperidone treated subjects achieved remission of delirium within 72 hours. 2. DRS total scores reduced and average of 45.3% within 72 hours, p<.05.	Not reported

Table S3: Cholinesterase inhibitor trials for the treatment of delirium (reference numbers refer to references listed at the end of this document).

SM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed (71), ICU=intensive care unit, CAM-ICU=Confusion Assessment Method for The ICU (72), LOS=length of stay, CAM=Confusion Assessment Method (75), NA=not applicable, DSI=Delirium Symptom Interview (83), MDAS=Memorial Delirium Assessment Scale (80).

Note: All reported differences were statistically significant, unless stated otherwise.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Liptzin et al. 2005 (21)	Donepezil 5 mg daily or placebo for 14 days administered pre-operatively and continued for 14 days following surgery. The dose of donepezil was increased to 10 mg daily or matched placebo when symptoms of delirium presented.	Geriatric patients (mean age=67.2) undergoing elective total joint arthroplasty of the knee or hip. Prevalence of pre-operative delirium not reported.	Donepezil (N) = 39 Placebo (N) = 41	Randomized, double blind, placebo controlled, parallel two arm trial Fixed dosing regimen.	No	DSM-IV, CAM and DSI	No risk prediction model used.	Not reported	Not reported	1. No difference in proportion of donepezil treated subjects diagnosed with post-operative delirium compared to placebo. 2. No difference in proportion subjects diagnosed with post-operative subsyndromal delirium between treatment groups. 3. No differences in duration of delirium episodes.	1. No differences in ICU LOS. 2. No differences in total hospital LOS. 3. No differences in proportion of subjects discharged to a rehabilitation facility.
Zaslavsky et al. 2012 (24)	Pre-operative transdermal rivastigmine 5-cm^2 or placebo patch.	Geriatric patients (age>65) admitted for elective surgery under general anesthesia and at risk for post-operative delirium. Prevalence of pre-operative delirium not reported.	Rivastigmine (N) = 11 Placebo (N) = 17	Randomized, double blind, placebo controlled, parallel two arm trial Fixed dosing regimen.	No	CAM	Presence of at least <u>one</u> of five predictive factors: (1) preoperative cognitive impairment, (2) age>70 years, (3) preoperative use of psychoactive drugs, (4) history of prior delirium; (5) severe illness or comorbidity.	Not reported	Not reported	No difference in proportion of rivastigmine treated subjects diagnosed with post-operative delirium compared to placebo.	Not reported
Sampson et al. 2007 (22)	Donepezil 5 mg or placebo administered immediately post-operatively and daily following surgery for three days.	Geriatric patients (mean age=67.8) undergoing elective total hip replacement. Prevalence of pre-operative delirium not reported.	Donepezil (N) = 19 Placebo (N) = 14	Randomized, double blind, placebo controlled, parallel two arm trial Fixed dosing regimen.	No	DSI	NA	Not reported	DSI	1. Trend level lower proportion of donepezil treated subjects diagnosed with post-operative delirium compared to placebo (9.5% vs. 35.7%), p=.08. 2. No differences in duration of delirium episodes. 3. Trend level lesser severity of delirium symptoms for donepezil treated subjects compared to placebo (by DSI scores at all time points: values not presented, p=.05).	Trend level shorter total hospital LOS for the donepezil treated subjects compared to placebo (mean days: (9.9 vs. 12.1), p=.09.
Gamberini et al. 2009 (25)	Rivastigmine 1.5 mg every 8 hours or placebo administered starting the evening before surgery and continued until the evening of the sixth post-operative day.	Geriatric patients (age>65) undergoing elective cardiac surgery with cardiopulmonary bypass. Baseline prevalence rates of delirium no reported.	Rivastigmine (N) = 59 Placebo (N) = 61	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	No	CAM	No risk prediction model used.	Not reported	Not reported	1. No difference in proportion of rivastigmine treated subjects diagnosed with post-operative delirium compared to placebo. 2. No differences in duration of delirium episodes.	1. No differences in ICU LOS. 2. No differences in total hospital LOS.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
van Eijk et al. 2010 (45)	ICU patients received an increasing dose of rivastigmine or placebo titrated to 6 mg twice daily over 9 days, treatment continued until resolution of delirium or hospital discharge. Subjects in both treatment groups received concomitant IV haloperidol 1 mg or 2.5 mg three times daily (depending on age).	Geriatric ICU patients (mean age=69) with delirium.	Rivastigmine (N) = 54 Placebo (N) = 50	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	A greater proportion of rivastigmine treated subjects (85%) compared to placebo treated subjects (64%) were emergently admitted to the ICU.	CAM-ICU	NA	CAM-ICU negative for 48 hours (2 consecutive ratings)	DSI	1. Trend level longer duration of delirium episodes for the rivastigmine treated subjects compared to placebo treated subjects (median days: 5 vs. 3), p= .06. 2. Significantly greater severity of delirium symptoms for rivastigmine treated subjects compared to placebo: (median of mean DSI scores=2.3 vs. 2), p=.004.	1. Significantly longer ICU LOS for rivastigmine treated subjects compared to placebo (median days:15 vs. 8), p<.001. 2. Trend level longer total hospital LOS for rivastigmine treated subjects compared to placebo (median days:29 vs. 26), p=.06. 3. Trend level higher hospital mortality rates for the rivastigmine treated subjects compared to placebo (22% vs. 8%), p=.07.
Marcantonio et al. 2011 (23)	Donepezil 5 mg or placebo administered within 24 hours of surgery, either pre-operatively or post-operatively, and 5 mg/day of donepezil or placebo continued for 30 days or until side effects or the clinical situation required termination.	Geriatric patients (age>70) admitted to an orthopedics for surgical repair of hip fracture. Delirium was present at baseline in 1/7 donepezil treated and in 4/9 placebo treated subjects.	Donepezil (N) = 7 Placebo (N) = 9	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	Higher pre-operative prevalence of delirium in the placebo treated group (44%) compared to the donepezil treated group (14%).	MDAS and CAM	No risk prediction model used.	Not reported.	MDAS	1. No difference in incidence of post-operative delirium between donepezil and placebo treated subjects. 2. No differences in severity of delirium symptoms.	Not reported

Table S4: Treatment trials of the effects of anesthetic technique, peri-operative analgesia and, peri-operative and critical care sedation in delirium (reference numbers refer to references listed at the end of this document).

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed (71), IV=intravenous, ICU=intensive care unit, CAM-ICU=Confusion Assessment Method for The ICU (72), LOS=length of stay, DSM-III=Diagnostic and Statistical Manual of Mental Disorders, 3rd ed (84), DRS-R–98=Delirium Rating Scale-Revised–98 (74), CAM=Confusion Assessment Method (75), ICDSC=Intensive Care Delirium Screening Checklist (76), DSM-IV-TR=Diagnostic and statistical manual of mental disorders, 4th ed., text rev (78), FICB=fascia iliaca compartment block, PCA=patient controlled analgesia, POD=postoperative day, RASS=Richmond Agitation-Sedation Scale (85).

Note: All reported differences were statistically significant, unless stated otherwise.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Berggren et al. 1987 (26)	Patients undergoing surgical repair of femoral neck fracture received either epidural (prilocaine and bupivacaine if necessary) or general (halothane with thiopental induction) anesthesia.	Geriatric patients (age>64) admitted to orthopedic units with femoral neck fracture for surgical repair. 3/28 subjects receiving epidural and 2/29 subjects receiving general anesthesia were diagnosed with pre-operative delirium.	Epidural anesthesia (N) = 28 Halothane anesthesia (N) = 29	Randomized, single blind, parallel two arm, active comparator trial. Dosing standardized per clinical practice.	Anticholinergic drugs used more frequently in the epidural compared to the halothane anesthesia group.	DSM-III	No risk prediction model used	Not reported	Not reported	No difference in incidence of post-operative delirium between epidural and halothane anesthesia groups.	No differences in total hospital LOS.
Papaioannou et al. 2005 (27)	Patients undergoing elective surgery received either general or regional anesthesia (epidural or spinal) with or without conscious sedation by propofol infusion.	Geriatric patients (age>60) undergoing elective surgery. Baseline prevalence rates of delirium not reported.	General anesthesia (N) = 28 Regional anesthesia (N) = 19	Randomized, parallel two arm, active comparator trial. Dosing standardized per clinical practice. Blinding of raters not reported.	A greater proportion of general anesthesia subjects received post-operative IV analgesia compared to the local anesthesia group.	DSM-III	No risk prediction model used	Not reported	Not reported	No difference between regional and general anesthesia groups in proportion of subjects diagnosed with post-operative delirium.	No differences in total hospital LOS.
Mouzopoulos et al. 2009 (29)	Patients undergoing surgical repair of hip fracture received either Iliac fascia compartment block (FICB) (0.3 mL/kg bupivacaine) or placebo FICB pre-operatively and repeated once daily post-operatively until delirium occurrence or discharge.	Geriatric patients (age≥70) admitted to an orthopedic unit for surgical repair of hip fracture at intermediate or high risk for delirium. Subjects diagnosed with pre-operative delirium were excluded.	FICB prophylaxis (N) = 102 Placebo (N) = 105	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	Greater amount of IM pethidine (meperidine) administered to the placebo group for peri-operative pain control compared to the FICB group.	DSM-IV and CAM	Inouye prediction model (1993;1996)	Not reported	DRS-R-98	1. Incidence of post-operative delirium “significantly” lower in the FICB group compared to the placebo group (10.78% vs. 23.8%), p-not reported. 2. Duration of delirium episodes significantly shorter in the FICB group compared to placebo (mean days: 5.22 versus 10.9), p<.001. 3. Severity of delirium symptoms significantly less in the FICB group compared to the placebo (highest DRS-R-98 value: 14.34 vs. 18.61), p<.001.	Not reported

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Beaussier et al. 2006 (28)	Patients undergoing surgical resection of cancer of the left colon or rectum received pre-operatively either intrathecal morphine (300 μg) via the L4-L5 inter-space or 3ml saline injected in the subcutaneous space at the L4-L5 level. Post-operatively, both groups received IV boluses and PCA morphine for post-operative pain management.	Geriatric patients (age>70) admitted for surgical resection of cancer of left colon or rectum. Baseline prevalence rates of delirium not reported.	Intrathecal morphine + IV PCA (N) = 26 IV PCA only (N) = 26	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	Daily post-operative IV PCA morphine consumption was lower in the intrathecal morphine group compared to placebo.	CAM	No risk prediction model used	Not reported	Not reported	No difference in proportion of subjects diagnosed with post-operative delirium between the intrathecal morphine and placebo groups.	No differences in total hospital LOS.
Leung et al, 2006 (30)	Patients undergoing spinal surgery with general anesthesia received either gabapentin 900 mg or placebo orally 1 to 2 hours before surgery, and continued daily for the first 3 post-operative days.	Older patients (mean age=59.6) undergoing surgery involving the spine, requiring general anesthesia. Baseline prevalence rates of delirium not reported.	Gabapentin (N) = 9 Placebo (N) = 12	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	Average daily dose of hydromorphone higher on POD 1 and POD 2 for the placebo treated group compared to the gabapentin group.	CAM	No risk prediction model used	Not reported	Not reported	Proportion of gabapentin treated subjects diagnosed with post-operative delirium significantly less compared to placebo (42% vs. 0%), p<.05.	Not reported
Riker et al. 2009 (31)	Mechanically ventilated ICU patients received either a continuous IV infusion of a flexible dose of dexmedetomidine (0.2-1.4 μg/kg/hour) or midazolam (0.02-0.1 mg/kg/hour) titrated to achieve light sedation from enrollment until extubation or 30 days.	Older medical and surgical ICU patients (mean age=62) who were mechanically ventilated. 60.3% of dexmedetomidine and 59.3% of midazolam treated subjects were diagnosed with delirium at baseline.	Dexmedetomidine (N) = 244 Midazolam (N) = 122	Randomized, double blind, parallel two arm, active comparator trial. Flexible dosing regimen.	No	CAM-ICU	No risk prediction model used	Not reported	Not reported	1. Dexmedetomidine treatment in subjects delirium-free at baseline was associated with a 15.4% decrease (p=.02), with a lesser delirium prevalence for dexmedetomidine compared to midazolam (32.9% vs. 55.0%), p=.03. 2. The effect of dexmedetomidine in subjects with delirium at baseline was a 32.2% reduction (p<.001), with a lesser delirium prevalence for dexmedetomidine compared to midazolam (68.7% vs. 95.5%), p<.001. 3. Greater number of mean delirium-free days for dexmedetomidine treated subjects compared to midazolam (2.5 vs 1.7), p=.002.	1. No differences in ICU LOS. 2. No differences in all cause 30 day mortality rates. 3. Time to extubation shorter for dexmedetomidine treated subjects compared to midazolam (median days: 3.7 vs. 5.6), p=.01.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Reade et al. 2009 (20)	Mechanically ventilated ICU patients received either a continuous IV infusion of a flexible dose of dexmedetomidine (0.2 to 0.7 µg/kg/hour) or haloperidol (0.5 to 2 mg/hour) for as long as deemed necessary by the treating physician.	Middle aged mechanical ventilation aged medical and surgical ICU patients in whom extubation was not possible solely because of agitation. 30% of dexmedetomidine and 40% of haloperidol treated patients were diagnosed with delirium at baseline. 50% of dexmedetomidine and 60% of haloperidol treated patients were diagnosed with subsyndromal delirium at baseline.	Dexmedetomidine (N) = 10 Haloperidol (N) = 10	Randomized, open label, parallel two arm, active comparator trial. Flexible dosing regimen.	1. Median age=52 for dexmedetomidine and 68 for Haloperidol, p=.241. 2. Requiring physical restraint prior to enrollment: dexmedetomidine=80%, haloperidol=50%, p=0.160.	ICDSC score≥4	No formal risk prediction model used. However, a significant proportion of subjects at elevated risk by carrying Subsyndromal delirium diagnosis (ICDSC total score of 1-3)	ICDSC score<4	Not reported	No differences in duration of delirium episodes between dexmedetomidine treated compared to haloperidol (median hours to achieve a ICDSC score < 4 (0 vs. 0), p=.50.	1. ICU LOS shorter for dexmedetomidine treated subjects compared to haloperidol (median days:4.5 vs. 6), p=.009. 2. No differences in hospital mortality rates. 3. Time to extubation shorter for dexmedetomidine treated subjects compared to haloperidol (median hours:19.9 vs. 42.2), p=.01.
Pandharipande et al. 2007 (33)	Mechanically ventilated ICU patients received either IV dexmedetomidine infusion started at 0.15 µg/kg/hour and titrated to a maximum of 1.5 µg/kg/hour or lorazepam infusion started at a dose of 1 mg/hour and titrated to a maximum of 10 mg/hour to achieve the sedation goal set by the patient's medical team using the RASS. Treatment continued until extubation or for the maximum time of 120 hours.	Adult (median age=60) medical and surgical ICU patients requiring mechanical ventilation for longer than 24 hours. Baseline prevalence rates of delirium not reported.	Dexmedetomidine (N) = 52 Lorazepam (N) = 51	Randomized, double blind, parallel two arm, active comparator trial. Flexible dosing regimen.	No	RASS score of minus 3 or greater (i.e., RASS −3, −2, −1, 0, etc.; i.e., responsive to verbal stimulus) and CAM-ICU	No risk prediction model used	Not reported	Not reported	1. No difference in proportion of subjects diagnosed with delirium during follow-up between dexmedetomidine and lorazepam treated subjects. 2. No differences in duration of delirium episodes.	1. No differences in ICU LOS. 2. No differences in 28 day mortality rates. 3. No differences in 12 month mortality rates. 4. No difference in ventilator free days. 5. Smaller proportion of dexmedetomidine treated subjects experienced coma compared to lorazepam (63% vs. 92%), p<.001.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Maldonado et al. 2009 (32)	Patients who underwent elective cardiac surgery received one of three post-operative sedation protocols: 1. Dexmedetomidine loading dose of 0.4 μg/kg, followed by a maintenance IV infusion ranging from 0.2 μg/kg/hour to 0.7 μg/kg/hour, continuing post-extubation as deemed clinically necessary for a maximum of 24 hours. 2. Propofol maintenance IV infusion ranging from 25 μg/kg/minute to 50 μg/kg/minute, discontinued prior to extubation. 3. Midazolam maintenance IV infusion ranging from 0.5 mg/hour to 2 mg/hour, discontinued prior to extubation.	Mechanically ventilated older ICU patients (mean age=57.7) post elective cardiac surgery with cardiopulmonary bypass. Baseline prevalence rates of delirium not reported.	Dexmedetomidine (N) = 36 Midazolam (N) = 32 Propofol (N) = 31	Randomized, open label, parallel three arm, active comparators trial. Flexible dosing regimen.	No	DSM-IV–TR	No risk prediction model used	Not reported	Not reported	1. Lower proportion of dexmedetomidine treated subjects diagnosed with post-operative delirium compared to both propofol and midazolam (10% vs. 44% vs. 44%), p<.001 (ITT analysis). 2. No differences in duration of delirium episodes.	1. No differences in ICU LOS. 2. No differences in total hospital LOS. 3. No differences in time to extubation.
Shehabi et al. 2009 (34)	Mechanically ventilated ICU patients received post-operatively either a dexmedetomidine maintenance IV infusion ranging from 0.1 μg/kg/hour to 0.7 μg/kg/hour or a morphine maintenance infusion ranging from 10 μg/kg/hour to 70 μg/kg/hour, and was continued until subject was ready to discharge from ICU or to a maximum of 48 hours of mechanical ventilation.	Geriatric patients (age>60) post-operative from on pump cardiac surgery (coronary artery bypass graft and/or valve replacement), mechanically ventilated in the ICU. Baseline prevalence rates of delirium not reported.	Dexmedetomidine (N) = 152 Morphine (N) = 147	Randomized, double blind, parallel two arm, active comparator trial. Flexible dosing regimen.	No	CAM-ICU	No risk prediction model used	Delirium free for more than 24 hours = two consecutive negative CAM-ICU ratings.	Not reported.	1. Trend level smaller proportion of dexmedetomidine treated subjects with post-operative delirium compared to morphine (8.6% vs. 15%), p=.08. 2. Duration of delirium episodes shorter in the dexmedetomidine treated group compared with morphine (median days: 2 vs. 5), p=.03.	1. No differences in ICU LOS. 2. No differences in total hospital LOS. 3. No differences in hospital mortality rates. 4. Shorter time to extubation for dexmedetomidine treated subjects compared to morphine (median hours: 14 vs. 15), p=.03.

Table S5: Treatment trials of miscellaneous pharmacological agents in delirium (reference numbers refer to references listed at the end of this document).

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed (71), IV=intravenous, ICU=intensive care unit, LOS=length of stay, CAM=Confusion Assessment Method (75), ICDSC=Intensive Care Delirium Screening Checklist (76), MDAS=Memorial Delirium Assessment Scale (80), DRS=Delirium Rating Scale (79), NA=not applicable, CABG=coronary artery bypass graft.

Note: All reported differences were statistically significant, unless stated otherwise.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Al-Aama et al. 2011 (39)	Acute medical patients received either 0.5 mg of oral melatonin or placebo prior to sleep daily until discharge, death or up to 14 days.	Geriatric (age>65) acute medical inpatients. Baseline delirium diagnosed in 14.7% of subjects in the placebo group and 8.2% of subjects in the melatonin group.	Melatonin (N) = 72 Placebo (N) = 73	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	No	CAM	No risk prediction model used	Not reported	MDAS	1. Lower prevalence of delirium in the melatonin treatment group compared to the placebo group. (12.0% vs. 31.0%), p<.01. 2. No differences in severity of delirium symptoms.	1. No differences in total hospital LOS. 2. No differences in hospital mortality rates. 3. No differences in need for sedation or physical restraint.
Yang et al. 2012 (70)	Delirious general hospital patients received either flexible dosing risperidone alone or flexible dosing risperidone plus one hour of bright light exposure by a light box with an intensity of 10,000 lux daily (7 AM - 8 AM) for five days.	Geriatric (mean age=69.6) delirious hospitalized medical and surgical patients.	Risperidone alone (N) = 16 Risperidone with bright light therapy (N) = 20	Randomized, open label, parallel single arm trial. Fixed dosing regimen.	1. Baseline DRS scores higher for the risperidone only group compared to the risperidone + bright light therapy group. 2. Trend level baseline MDAS scores higher for the risperidone only group compared to the risperidone + bright light therapy group. 3. Baseline sleep efficiency (percent sleep of total bed time) better for the risperidone only group than the risperidone + bright light therapy group.	DSM-IV	NA	Not reported	DRS and MDAS	More rapid decrease in delirium symptom severity scores for the risperidone + bright light group compared to the risperidone alone group. (Reflected in DRS total scores over time, but not in MDAS scores), p<.05).	Greater improvement in sleep efficiency in the risperidone + bright light therapy group compared to the risperidone alone group, data not provided, p=.002.
Hudetz et al. 2009 (38)	Patients undergoing cardiac surgery with cardiopulmonary bypass received single IV dose of either ketamine (0.5 mg/kg) or placebo (0.9% saline) during anesthetic induction.	Male geriatric patients (mean age=64) undergoing elective CABG or valve repair/replacement with cardiopulmonary bypass. Baseline prevalence rates of delirium not reported.	Placebo (N) = 29 Ketamine (N) = 29	Randomized, double blind, placebo controlled, parallel two arm trial. Fixed dosing regimen.	No	ICDSC≥4	No risk prediction model used	Not reported	ICDSC	Lower proportion of ketamine treated subjects diagnosed with post-operative delirium compared to placebo (3.4% vs. 31%), p<0.01.	1. No differences in ICU LOS. 2. No differences in total hospital LOS. 3. No differences in time to extubation. 4. Smaller proportion ketamine treated subjects re-admitted to the hospital during a 30 day post-operative follow-up compared to placebo (6.9% vs. 27.6%), p<.05.

Study	Intervention	Study Subjects	Number of Subjects Randomized And Received Intervention	Study Design	Intervention Group Imbalances	Method for Diagnosing Delirium	Delirium Risk Prediction Model	How Delirium Episode Resolution Was Determined	Method for Assessing Delirium Severity	Delirium Specific Outcomes	Delirium Non-Specific Outcomes
Sieber et al. 2010 (37)	Patients undergoing hip fracture repair under spinal anesthesia received either intraoperative propofol-based light sedation or propofol-based deep sedation. Bispectral index (BIS) monitoring of the electroencephalogram was used to assess the depth of sedation. Deep sedation BIS = 50, light sedation BIS $\geq$ 80.	Geriatric patients (age>65) without pre-operative delirium undergoing hip fracture repair.	Deep sedation (N) = 57 Light sedation (N) = 57	Randomized, double blind, parallel two arm, active comparator trial. Randomization stratified for age (>80 years or 65-80 years) and cognitive impairment (MMSE score, 24-30 or 15-23). Flexible dosing regimen according to sedation depth.	1. Longer mean duration of surgery for the deep sedation group compared to the light sedation group. 2. Greater proportion of subjects in the light sedation group receiving intra-operative midazolam compared to the deep sedation group. 3. When intra-operative midazolam was given the light sedation group received a higher dose compared to the deep sedation group.	CAM	Subject selection not based a priori delirium risk assignment. Post hoc analysis demonstrated an Inouye (1993;1996) median risk = 2 points (intermediate risk) for both treatment groups.	Not reported.	Not reported	1. Lower incidence of post-operative delirium in in the light sedation group compared to the deep sedation group (19% vs. 40%), p<.05. 2. No differences in duration of delirium episodes.	1. No differences in ICU LOS. 2. No differences in total hospital LOS. 3. No differences in hospital mortality rates.

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