Delirium in Cancer:
Psychopharmacologic Management

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Delirium in Patients with Cancer

- Prevalence ranges from 15% - 30% in hospitalized cancer patients
- Highly prevalent in the last weeks of life (40% - 85%)
- Associated with increased morbidity/distress in patients, family, staff
- Interferes with symptom assessment and control
Delirium in Patients with Cancer

- Delirium is under-recognized and under-treated.
- One of the barriers to adequate clinical intervention in delirium is the lack of appreciation for the distress experienced by patients with delirium, as well as the impact of delirium on spouses/caregivers and staff.
- We suspect that patients with hypoactive delirium are perceived to be in less distress than agitated patients with hyperactive delirium.
DSM-IV Criteria for Delirium

A. Disturbance of consciousness (i.e., disturbance of awareness of the environment) with reduced ability to focus, sustain or shift attention

B. Change in cognition (such as memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a pre-existing, established or evolving dementia
C. The disturbance evolves over a short period of time (usually hours to days) and tends to fluctuate during the course of the day

D. There is evidence from the history, physical examination, or laboratory findings of a general medical condition judged to be etiologically related to the disturbance
Subtypes of Delirium

Delirium is a disturbance of arousal and cognition.

Subtypes of delirium are based on the type of arousal disturbance:

- Hyperactive
- Hypoactive
- Mixed
Subtypes of Delirium

- In 12 studies, the prevalence of each of the subtypes of delirium has varied widely.
- A meta-analysis of these studies suggest the following average prevalence for each subtype:
  - Hypoactive: 48% (ranges: 15-71%)
  - Hyperactive: 24% (ranges: 13-46%)
  - Mixed: 36% (ranges: 11-55%)
Hypoactive Delirium: Controversies and Barriers to Treatment

• Hypoactive Delirium is thought to be very rare, but in fact accounts for an average of 50% of delirium cases.
• Hypoactive Delirium is thought not to cause morbidity and therefore does not require pharmacologic intervention.
• Hypoactive Delirium, because of its phenomenologic differences with Hyperactive Delirium, is thought not to respond to pharmacologic interventions with neuroleptics.
The Delirium Experience

William Breitbart, M.D.
Christopher Gibson, PhD.
Annie Tremblay, M.D.
Memorial Sloan-Kettering Cancer Center

Breitbart et al, Psychosomatics, 2002
Objectives

- To describe the experience of delirium in hospitalized cancer patients.
- To examine the level of distress related to the delirium experience in cancer patients, their spouses/caregivers, and nurses.
- To examine the relationships among delirium-related distress, delirium phenomenology, etiology, demographic and medical variables.
Delirium Experience Questionnaire

- Do you remember being confused? Yes__ No__
- If no, are you distressed that you can’t remember? Yes__ No__
- How distressed? 0-4 numerical rating scale (NRS)
- If yes, was the experience distressing? Yes__ No__
- How distressing? 0-4 NRS
- Can you describe the experience?
- Spouse /Caregiver: How distressed were you during the patient’s delirium? 0-4 NRS
- Nurse: Your patient was confused. Did you find it distressing? 0-4 NRS
- 0-4NRS: 0: not at all, 4: extremely
Sample Characteristics (n= 101)

- Mean Age: 58.36 years (SD= 16.6)
- Gender: Males= 52; Females= 49
- Race: White= 67%; Black= 21%; Hispanic= 9%; Other=3%
- Cancer Diagnoses: Lung-21%, GI-14%, Lymphoma-13% Breast-11%, Head and Neck-6%, Ovarian-4%, Brain-3%, Other cancers- 28%
- Stage: Localized=16%, Metastatic=79%, Terminal=5%
- Brain Metastases: 24%; History of Dementia: 18%
- Karnofsky: Mean= 35.5 (SD=7.7)
Sample Characteristics (n= 101)

- Memorial Delirium Assessment Scale (MDAS):
  Mean MDAS = 19 (SD 3.2), range 14-30
- Delirium Subtypes: Hypoactive= 53%; Hyperactive=47%
- Delirium Etiologies:
  Multiple causes= 74%; Single cause= 26%
- Delirium Etiologies encountered:
  Opioids-65%, infection-39% steroids-30%, hypoxia-26%, dehydration-12%, CNS-12%, Other-13%
Results

- 53.5% of patients (N=54) who recovered from delirium remember being delirious.
- 93% of patients who remember being delirious report the experience as being “distressing”.
- Mean level of patient distress (0-4 NRS)= 3.22 (SD=.86)
- Mean level of Spouse/Caregiver distress= 3.75 (SD=.47)
- Mean level of Nurse distress= 3.09 (SD=.77)
Logistic Regression Analysis of Predictors of Delirium Recall in Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term Memory Impairment</td>
<td>.001</td>
<td>38.4</td>
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<tr>
<td>MDAS Total Score</td>
<td>.02</td>
<td>11.3</td>
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<tr>
<td>Perceptual Disturbance</td>
<td>.002</td>
<td>6.9</td>
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</table>

OR = Odds Ratio
Percentage of Patients with Delirium Recall Based Upon Delirium Severity.
## Logistic Regression Analysis of Predictors of Patient, Spouse/Caregiver, and Nurse Distress

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<thead>
<tr>
<th>Variable</th>
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<tbody>
<tr>
<td><strong>Patient Distress</strong></td>
<td></td>
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<tr>
<td><em>Delusions</em></td>
<td>.05</td>
<td>7.9</td>
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<tr>
<td><strong>Spouse/Caregiver Distress</strong></td>
<td></td>
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</tr>
<tr>
<td><em>Karnofsky (KPS)</em></td>
<td>.003</td>
<td>9.1</td>
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<tr>
<td><strong>Nurse Distress</strong></td>
<td></td>
<td></td>
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<tr>
<td><em>MDAS Total Score</em></td>
<td>.01</td>
<td>5.2</td>
</tr>
<tr>
<td><em>Perceptual disturbances</em></td>
<td>.04</td>
<td>3.6</td>
</tr>
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OR = Odds Ratio
Distress in Hyperactive vs Hypoactive Delirium

- There were no significant differences in the report of distress for patients, or nurses based on subtype of delirium. Spouses/caregivers were more distressed by hypoactive delirium.

- Hypoactive delirium was equally as distressing as Hyperactive delirium for patients, nurses.
Summary: Delirium Experience

- Delirium is a highly distressing experience for patients, spouses/caregivers and nurses.
- Delirium is especially distressing when delirium is more severe and is characterized by the presence of delusions and hallucinations.
- Hypoactive delirium is as distressing as hyperactive delirium.
- Delirium is important to treat because it is associated with significant suffering not only in patients, but also in spouses/caregivers and staff.
Delirium Assessment Methods

Diagnostic classification systems
- DSM-III, DSM-III-R, DSM-IV
- ICD-9, ICD-10

Diagnostic interview instruments
- Delirium symptom interview (DS)
- Confusion Assessment Method (CAM)

Delirium rating scales
- Delirium Rating Scale (DRS)
- Confusion Rating Scale (CRS)
- Memorial Delirium Assessment Scale (MDAS)

Cognitive impairment screening scales
- Mini-Mental State Exam (MMSE)
- Short Portable Mental Status Questionnaire (SPMSQ)
- Cognitive Capacity Screening Examination Test (BOMC)
Memorial Delirium Assessment Scale (MDAS)

- REDUCED LEVEL OF CONSCIOUSNESS (AWARENESS)
- DISORIENTATION
- SHORT-TERM MEMORY IMPAIRMENT
- IMPAIRED DIGIT SPAN
- REDUCED ABILITY TO MAINTAIN AND SHIFT ATTENTION
- DISORGANIZED THINKING
- PERCEPTUAL DISTURBANCE
- DELUSIONS
- DECREASED OR INCREASED PSYCHOMOTOR
- SLEEP-WAKE CYCLE DISTURBANCE (DISORDER OF AROUSAL)

Breitbart, et al, JPSM, 1996
Validation of the Memorial Delirium Assessment Scale in the Terminally Ill

• The MDAS is a 10 item delirium severity and diagnostic instrument designed for repeated assessment and treatment evaluation
• Two validation studies have been conducted to date using large samples of hospitalized cancer and AIDS patients as well as cancer patients admitted to a palliative care unit
• The MDAS is highly correlated with other diagnostic measures of delirium (e.g. the DRS) and cognition (e.g. the MMSE)
• Diagnostic cut-off scores of 13/30 in hospitalized cancer patients, and 7/30 in PCU patients have been suggested
• Prorating item scores is necessary in up to 20% of patients

Overview of Delirium Management

**DELIRIUM**  |  **TREATMENT**  |  **OUTCOME**
--- | --- | ---
Pre Terminal Delirium | Aimed at reversing etiology | Delirium is reversible
Terminal Delirium | Aimed at controlling symptomatology | Delirium is irreversible
Assessment of Etiologies of Delirium in Advanced Cancer Patients

• Unclear or never discovered in over 50% of patients
• Three or more etiologies usually present
• Irreversible 30-40% of the time, especially in the terminally ill
• Etiology found in 40% - 50% of cases
  – 30% - 70% improve with treatment of etiology
Assessment of Etiologies of Delirium in the Advanced Cancer Patient (cont’d)

- Diagnostic work-up must be consistent with the goals of care
  - minimally invasive in the terminally ill
  - treatments are effective and/or minimally burdensome or distressing
Causes of Delirium in Advanced Cancer

**Direct**
- Primary brain tumor
- Metastatic spread

**Indirect**
- Hypoxia
- Metabolic encephalopathy due to organ failure
- Electrolyte imbalance
- Withdrawal states
Causes of Delirium in Cancer Patients (cont’d)

Indirect (cont’d)
Treatment side effects from
  Chemotherapeutic agents, steroids,
    biological response modifiers
  Radiation
  Opioids
  Anticholinergics
  Antiemetics
Infection
Hematologic abnormalities
Nutritional deficiencies
Paraneoplastic syndromes
Non-Pharmacological Interventions for Delirium in the Advanced Cancer Patient

1. Provide safe and supportive environment for patient, staff, and family

2. Reassure family of the medical nature of delirium. Their family member is not “having a nervous breakdown”

3. Depending on stage of disease, either reassure family of transient nature of delirium or describe as a hallmark of approaching death
Non-Pharmacological Interventions for Delirium in Advanced Cancer (cont’d)

4. Provide proper sensory environment for patient
   — quiet, well-lit room
   — visible clock, calendar
   — familiar people, objects

5. Communicate with patient and family
   — goals of care and desirable outcomes, i.e., sedation vs. awake but agitated
   — regarding hallucinations and their management or meaning
# Pharmacological Management of Delirium

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<td>0.5-5 q2-12h</td>
<td>PO, IV, SC, IM</td>
</tr>
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<td>10-75 q4-8h</td>
<td>PO</td>
</tr>
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<td>12.5-50 q4-12h</td>
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<tr>
<td>Methotrimeprazine</td>
<td>12.5-50 q4-8h</td>
<td>IV, SC, PO</td>
</tr>
<tr>
<td>Droperidol</td>
<td>0.5-5 q12h</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Molindone</td>
<td>10-50 q8-12h</td>
<td>PO</td>
</tr>
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<tr>
<td><strong>Atypical Antipsychotics</strong></td>
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<tr>
<td>Risperidone</td>
<td>1-3 q12h</td>
<td>PO</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-5 q12h</td>
<td>PO/IM</td>
</tr>
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<td>Quetiapine</td>
<td>25-150 q12h</td>
<td>PO</td>
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<tr>
<td>Ziprasidone</td>
<td>20-80 q12h</td>
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<tr>
<td>Aripiprazolee</td>
<td>10-15 qd</td>
<td>PO</td>
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</table>
Side Effects of Neuroleptics/Antipsychotics

**Anticholinergic**
- Dry Mouth
- Constipation
- Cardiovascular (BP, QT interval)

**Antihistaminic**
- Sedation, Weight Gain

**Dopamine Blockade**
- Extrapyramidal Side Effects
- Hyperprolctinemia
- Neuroleptic Malignant Syndrome
Side Effects of Atypical Antipsychotics

Metabolic Syndrome
Hyperglycemia
Hyperlipidemia
Weight Gain
Olanzapine and Clozapine have highest incidence

QT Interval Prolongation
Torsade des Pointes
QTc prolongation beyond 500msec
ECG should be monitored daily during delirium RX
Consider interactions with other agents that prolong QT
## Side Effects of Haloperidol vs. Risperidone vs. Olanzapine

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Haloperidol</th>
<th>Risperidone</th>
<th>Olanzapine</th>
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<tbody>
<tr>
<td>EPS</td>
<td>&gt;30%</td>
<td>&gt;10%</td>
<td>&gt;2%</td>
</tr>
<tr>
<td>ACHE</td>
<td>&gt;2%</td>
<td>&gt;2%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Sedation</td>
<td>&gt;2%</td>
<td>&gt;10%</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>&gt;2%</td>
<td>&gt;30%</td>
<td>&gt;2%</td>
</tr>
<tr>
<td>Seizure</td>
<td>&gt;2%</td>
<td>&gt;2%</td>
<td>&gt;2%</td>
</tr>
</tbody>
</table>

Bezchlibnyk-Butler & Jeffries, 1999
Neurotransmitter/Receptor Effects of Antipsychotics

- Haloperidol: D2, α1
- Risperidone: 5HT2A, α1, α2, 5HT7, D2, 5HT3
- Olanzapine: 5HT2A, 5HT2C, 5HT3, 5HT6, D4, D3, D2, M1, H1, α1
Clinical Trials of Delirium Management

A double-blind, randomized trial of Haloperidol vs. Chlorpromazine vs. Lorazepam in the treatment of delirium in medically hospitalized AIDS patients with AIDS-related cancers (N=244 screened, 30 on trial.)

Results:
• Both Haloperidol and Chlorpromazine were effective in rapidly resolving the symptoms of delirium utilizing low dosage regimens
• Lorazepam alone was ineffective
• No clinically significant side effects
• Both hypoactive and hyperactive delirium responded to neuroleptics

Breitbart et al Am J Psy 1996
# AIDS Delirium Study

<table>
<thead>
<tr>
<th>Dose</th>
<th>Haloperidol</th>
<th>Chlorpromazine</th>
<th>Lorazepam</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.25 mg</td>
<td>10 mg</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>2</td>
<td>0.5 mg</td>
<td>20 mg</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>3</td>
<td>1.0 mg</td>
<td>40 mg</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>4</td>
<td>2.0 mg</td>
<td>80 mg</td>
<td>2.0 mg</td>
</tr>
<tr>
<td>5</td>
<td>2.5 mg</td>
<td>100 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>6</td>
<td>2.5 mg</td>
<td>100 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>7</td>
<td>2.5 mg</td>
<td>100 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>8</td>
<td>5.0 mg</td>
<td>200 mg</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>9</td>
<td>5.0 mg</td>
<td>200 mg</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Max</td>
<td>21.25 mg</td>
<td>850 mg</td>
<td>20.5 mg</td>
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All doses PO; Dose IM = 1/2 PO
Pharmacological Management of Delirium in AIDS Patients #02

Drug A

- Mini-Mental Status Exam Score
- Dose Level

Delirium Rating Scale Score

Hours Day 1

Time Post - Diagnosis

Days

0 1 2 3 4

3 16 15

22 15 15 15
AIDS DELIRIUM STUDY
Response to Treatment as Measured by DRS

Change in DRS from Baseline to End of Treatment
Significant Drug x Time Interactions
(F=4.40; df=2,27; p=.02)
AIDS DELIRIUM STUDY
Response to Treatment as Measured by MMSE

Change in MMSE Baseline to Day 2
No Significant Overall Drug x Time Interactions
AIDS DELIRIUM STUDY
EPS – Parkinsonian SXS

Mean rank order for ESRS Score:
- Haloperidol = 7.25
- Chlorpromazine = 3.50
- Lorazepam = 8.75

Extrapyramidal Symptom Rating Scale (ESRS)

Mean Score

Change in ESRS from Baseline thru Treatment

Pre Treatment During
Haloperidol (N = 11) (7.7)
Chlorpromazine (N = 13) (2.4)
Lorazepam (N = 6) (8.7)
# AIDS Delirium Study

## Drug Dosages

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Dose</th>
<th>Median Dose</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>2.6 mg</td>
<td>1.75 mg</td>
<td>0.75-6.25 mg</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100 mg</td>
<td>70 mg</td>
<td>30-257.5 mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>6.9 mg</td>
<td>3.0 mg</td>
<td>0.5-20 mg</td>
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1st 24 hours
# AIDS Delirium Study

## Drug Dosages

<table>
<thead>
<tr>
<th>Maintenance Dose</th>
<th>Days 2 - 7</th>
</tr>
</thead>
</table>
| **Haloperidol**  | mean dose 1.6 mg  
|                  | median dose 1.0 mg  
|                  | range 0.25 – 4.375 mg  |
| **Chlorpromazine** | mean dose 40 mg  
|                  | median dose 35 mg  
|                  | range 15 – 175 mg  |
| **Lorazepam**    | mean dose 1.5 mg  
|                  | median dose 1.25 mg  
|                  | range 1.25 – 2.0 mg  |
Neuroleptics for Hypoactive Delirium

- Both Haloperidol and Chlorpromazine were effective in improving the symptoms of delirium (as measured by the DRS) for both hyperactive (N=9), F=19.06, df=1.18, p<0.001, as well as hypoactive delirium (N=11), F=21.15, df=1.18, p<0.001.
An Open Trial of Olanzapine for the Treatment of Delirium in Hospitalized Cancer Patients

William Breitbart, M.D.
Annie Tremblay, M.D.
Christopher Gibson, Ph.D.
Memorial Sloan-Kettering Cancer Center
Efficacy of Olanzapine in the Treatment of Delirium

\[ t (\text{baseline}\,-\,\text{Time3}) = 10.1, \ p < .001 \]
Results- Olanzapine Efficacy

- Two MDAS cut-off scores were utilized to define delirium resolution:
  - MDAS below 13 at T3:
    - 78.7% improved on olanzapine
  - MDAS below 10 at T3:
    - 73.3% improved on olanzapine
Logistic Regression Analysis of Predictors to Olanzapine Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
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<tbody>
<tr>
<td>Age:</td>
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<tr>
<td>CNS Spread</td>
<td>.005</td>
<td>74.9</td>
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<tr>
<td>Subtype of Delirium</td>
<td>.01</td>
<td>11.3</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>.09</td>
<td>5.9</td>
</tr>
<tr>
<td>History of Dementia</td>
<td>.40</td>
<td>0.34</td>
</tr>
<tr>
<td>Delirium Severity</td>
<td>.1</td>
<td>5.03</td>
</tr>
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</table>

OR = Odds Ratio
Effect of Age on Olanzapine Response

Percent of Patients w/ MDAS < 10

Under 50 51-60 61-70 Over 70

X² = 22.8
p < .001
Efficacy of Olanzapine in Hypoactive and Hyperactive Delirium

F = 9.51
p < .003
Olanzapine Dosage

- Mean olanzapine dosage:
  - Baseline: 3.0 mgs (SD=0.14)
    range = 2.5 to 10 mgs
  - T2 (day2-3): 4.6 mgs (SD=0.27)
    range = 2.5 to 15 mgs
  - T3 (day4-7): 6.3 mgs (SD=0.52)
    range = 2.5 to 20 mgs
Olanzapine Side Effects

- Olanzapine side effects were common but rarely interfered with treatment or worsened delirium:

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>T1%</th>
<th>T2%</th>
<th>T3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>29%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>EPS</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>1.2%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3.7%</td>
<td></td>
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</table>
Clinical Trial of Risperidone for Delirium

A double-blind, randomized trial of Risperidone vs. Haloperidol in the treatment of delirium in 24 medically hospitalized cancer patients:

Results:

• Both Risperidone and Haloperidol were equally effective in resolving the symptoms of delirium utilizing low dosage regimens

• No significant difference in side effects

• Analysis and reporting of response rates, dosage regimens and side effects is insufficient, thus limiting the value of this trial

Han and Kim, Psychosomatics, 2004
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<td><strong>Novel Antipsychotics</strong></td>
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Pharmacological Management of Delirium (cont’d)

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<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5-2.0 q1-4h</td>
<td>PO, IV, IM</td>
</tr>
<tr>
<td>Midazolam</td>
<td>30-100 per 24h</td>
<td>IV, SC</td>
</tr>
<tr>
<td><strong>Anesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>10-50 q1h</td>
<td>IV</td>
</tr>
</tbody>
</table>
Pharmacological Management of Delirium Symptoms

Hyperactive agitated delirium

- Haloperidol IV/PO 2-10mg q4-12h & prn for agitation
- Add benztropine 0.5-1mg IV (po tid) for EPS
- Add lorazepam 0.5-2mg IV q4h for increased sedation
- Switch to chlorpromazine 25-50mg IV q4-12h for increased sedation
- Adjust dosage for optimal control of symptoms
- Switch to olanzapine if regimen not tolerated or if EPS is an issue

Continue indefinitely or until etiology is reversed and taper off slowly

Assess safety and assure safe environment

Identify and Treat Etiology

Delirium Diagnosed
Pharmacological Management of Delirium Symptoms

Delirium Diagnosed

Identify and Treat Etiology

Assess safety and assure safe environment

Hypoactive Delirium

Haloperidol PO/IV
0.5-6 mg q4-12h & prn for hallucinations/agitation

Add benztropine
0.5-1mg IV (po tid) for EPS

Reduce dose if sedated

Use olanzapine
2.5-5mg PO bid if EPS is an increasing concern

Continue indefinitely or until etiology is reversed and taper off slowly
Conclusions

• Delirium is a common neuropsychiatric complication in terminal cancer

• Psychiatrists must be familiar with the proper assessment, diagnosis, and management of delirium

• Appropriate management of delirium is important to minimize morbidity and improve quality of care
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Edited by Harvey M. Chochinov and William Breitbart

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