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Distinguishing Sedation From Efficacy in Antipsychotic Treatment

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Objectives

- To recognize the symptoms of acute agitation in an emergency department setting
- To understand the potential importance of minimizing sedation in the treatment of acute agitation in patients with schizophrenia
- To distinguish sedation from efficacy in antipsychotic treatment
- To understand the physiologic mechanisms for sedation and pharmacologic considerations when selecting an antipsychotic

Case Presentation

- William is a 37-year-old man who was found directing traffic in response to the instructions of a superior being
- Became agitated and violent when police approached
- Taken to Emergency Department (ED), where he was very agitated and responding to internal stimuli and combative toward staff
- Identified by a healthcare worker in the ED as someone with known schizophrenia

What would be your initial treatment consideration?

1. Malavade KE. *Psychiatry Weekly*. 2007;2(35). Available at: http://www.psychweekly.com/aspx/article/article_pf.aspx?articleid=578. Accessed Aug 20, 2014.

Initial Treatment Considerations and Goals for William[1]

Considerations for Patient[1]	Treatment Goals[1,2]
• Currently agitated and violent • Known history of schizophrenia and multiple hospitalizations • Unable to perform assessment of patient • Unable to determine vital signs	• Treat acute agitation • Prevent injury to self and others • Allow medical and psychiatric evaluations • Improve patient's comfort • Allow evaluation of underlying causes of agitation • Calm the patient down

1. Malavade KE. *Psychiatry Weekly*. 2007;2(35). Available at: http://www.psychweekly.com/aspx/article/article_pf.aspx?articleid=578. Accessed Aug 20, 2014.
2. Lehman et al. *Am J Psychiatry*. 2004;161(2 Suppl):1–56.

Definition of Agitation

- Agitation can be defined as excessive motor or verbal activity
- Agitation is not uncommon in untreated schizophrenia or bipolar mania
- Agitation associated with psychosis is a frequent reason for:
  - ED visits
  - Admission to a psychiatric inpatient facility
  - Continued hospitalization
- Despite treatment of the underlying psychiatric condition, intermittent agitated behavior can remain problematic

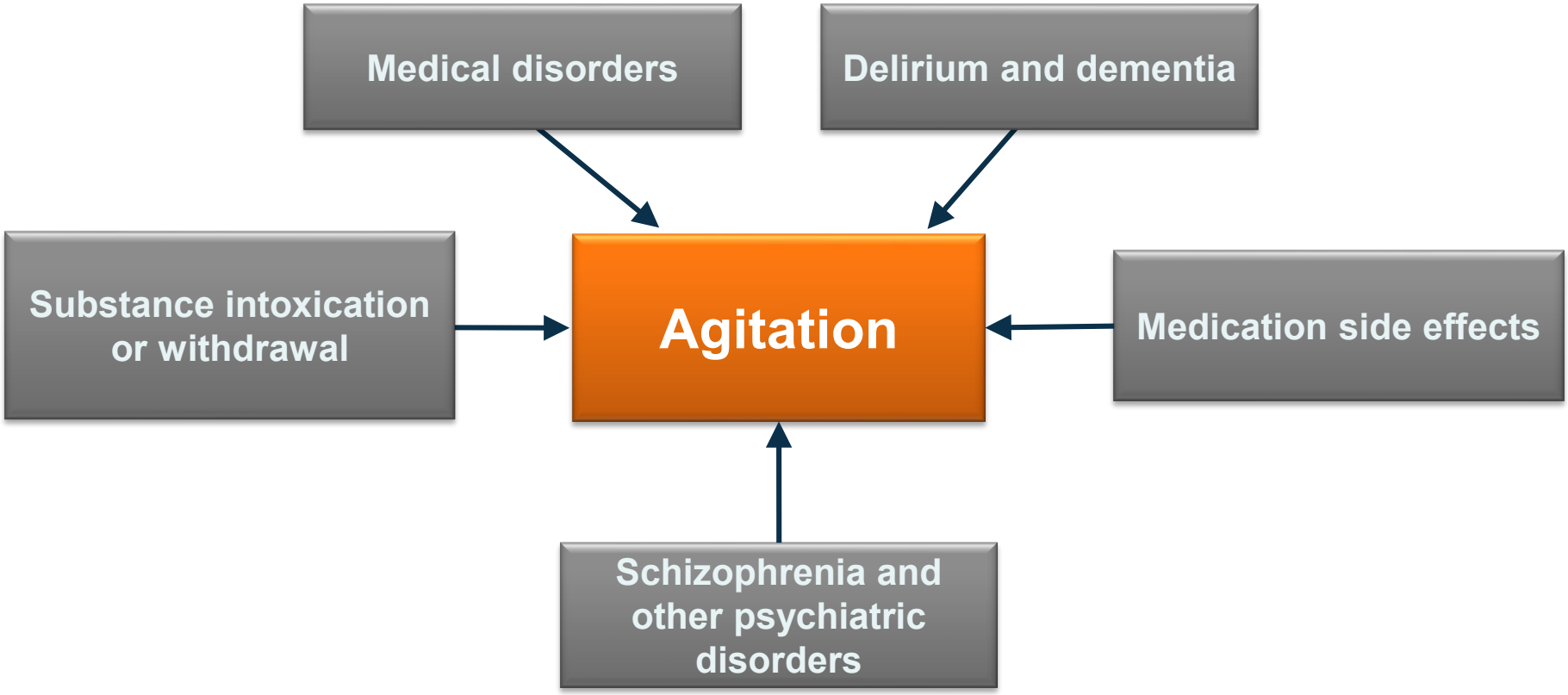
1. Citrome L. *Ther Clin Risk Manag*. 2013;9:235-245.

Examples of Agitation

- Excessive motor or vocal behavior
- Inappropriate or non-purposeful motor or vocal behavior
- Poorly organized and aimless psychomotor activity
- Strong emotions and heightened responsivity to stimuli

1. Schleifer JJ. *APT*. 2011;17:91–100.

Potential Reasons for Agitation in an Emergency Setting



1. Battaglia J et al. *CNS Spectrums*. 2007;12 (8 suppl 11):1-16.

Measuring Antipsychotic Efficacy

The measurement of efficacy of an antipsychotic may vary based on the clinical setting

	Perception of Efficacy
Research setting[1]	Positive and Negative Syndrome Scale (PANSS); Clinical Global Impression (CGI) scale
Acute phase[2]	Reduction of agitation and excitement (eg, the Agitation-Calmness Evaluation Scale [ACES], Corrigan Agitated Behaviour Scale [CABS]), PANSS Excited Component [PEC], Brief Psychiatric Rating Scale [BPRS])
Maintenance phase[3]	Maintenance of the therapeutic effect of the chosen antipsychotic and minimization of side-effect burden

1. Stroup TS et al. *Schizophr Res*. 2009;107:1-12.
2. Canas F. *Eur Neuropsychopharmacol*. 2007;17:S108-S114.
3. Kane JM et al. *J Clin Psychiatry*. 2008;69 (suppl1 1):18-31.

Sedation Versus Somnolence

- Sedation may:
  - Be caused by antagonism of muscarinic M_1, histamine H_1, and/or α_1-adrenergic receptors[1]
  - Lead to impaired psychomotor activity[1]
  - Contribute to impaired cognitive functioning, attention, memory and coordination[1]
  - Be manifested as feeling too tired to participate in activities, despite the desire to do so[2]
- Somnolence may:
  - Be distinct from sedation[1]
  - Be regulated by H_1 and α_1-adrenergic receptors[1]
  - Be manifested as sleepiness, drowsiness, and the need to sleep during the day[1]

In many cases, it is difficult to clinically differentiate between sedation and somnolence

1. Stahl SM. *Stahl's Essential Psychopharmacology*. 3rd edition. 2008. Cambridge University Press; New York, NY.
2. Miller DD. *Curr Psychiatry*. 2007;6(8):39-51.

Distinguishing Antipsychotic-related Sedation From Negative Symptoms

Example question: Ask the patient if he/she naps during the day or just lies around, and if they want to do things but cannot

Sedation	Wants to do things, but feels too tired; treatment might be dose reduction
Negative symptoms	Not interested in doing things; treatment might be a medication such as an SSRI
Cognitive impairment	Wants to do things but cannot organize themselves to do them; treatment might be cognitive training or remediation

SSRI, selective serotonin reuptake inhibitor.

1. Miller DD. *Curr Psychiatry*. 2007;6(8):39-51.

Sedation During Treatment of Acute Agitation: Potential Advantages

- Initiation of inpatient treatment in acute psychosis[1]
- Management of aggression, hostility, and violence[1]
- Initiation/maintenance in sleep disturbance or agitation/activation[1]
- Ameliorate insomnia and regulate patient's sleep-wake cycle[2]

1. Stahl SM. *Stahl's Essential Psychopharmacology*. 3rd edition. 2008. Cambridge University Press; New York, NY.
2. Kane JM et al. *J Clin Psychiatry*. 2008;69 (suppl1 1):18-31.

Sedation During Treatment of Acute Agitation: Potential Disadvantages

- May hinder diagnosis
- Could compromise patient evaluation and interfere with forming a therapeutic alliance
- Possibility that it is mistaken for negative symptoms or cognitive defects
- Could increase patient's negative feelings about medication, resulting in rejection of treatment

Calming patients rather than sedating them may be the most appropriate approach to managing agitation and aggression during acute psychiatric events

1. Canas F. *Eur Neuropsychopharmacol*. 2007;17:S108-S114.

Controlling Agitation Without Sedation

- When treating agitated patients, many clinicians consider calming effects and true antipsychotic effects to be one and the same, however:
  - Sedation may not be necessary to reduce symptoms of agitation
  - Studies of generally non-sedating short-acting injectable SGAs have shown that agitation and acute symptoms can by controlled without significant sedation
- The mechanisms of antipsychotics' therapeutic and sedative properties appear to be different

SGA, second-generation antipsychotic.

1. Miller DD. *Curr Psychiatry*. 2007;6(8):39-51.

Mechanisms for Sedation

- D_2-receptor antagonism may not be involved in causing sedation[1]
- Blocking 1 or more of the following is held theoretically responsible for causing sedation[2]:
  - M_1-muscarinic cholinergic receptors
  - H_1-histaminic receptors
  - α_1-adrenergic receptors
- All atypical antipsychotics are not equally sedating because they do not all have potent antagonist properties at the M_1-muscarinic cholinergic, H_1-histaminic, or α_1-adrenergic receptors[2]:
  - Agents with weaker antagonism of M_1-muscarinic cholinergic, H_1-histaminic, and α_1-adrenergic receptors may produce less sedation

1. Miller DD. *Curr Psychiatry*. 2007;6(8):39-51.
2. Stahl SM. *Stahl's Essential Psychopharmacology*. 4th edition. 2013. Cambridge University Press; New York, NY.

Pharmacologic Considerations When Selecting an Antipsychotics: Receptor Binding

Proposed Clinical Implications of Antipsychotic Receptor Activities

Receptor Activity	Possible Clinical Effects
D_2-receptor antagonism	Positive symptom alleviation, EPS, endocrine effects
5-HT_{2A} antagonism	Negative symptom alleviation, less EPS
High 5-HT_{2A}/D_2 binding affinity ratio	Better antipsychotic activity and lower EPS than D_2 antagonism alone
5-HT_{1A} agonism	Antidepressant and anxiolytic activity, improved cognition, reduced EPS, body weight changes
5-HT_{1D} antagonism	Antidepressant activity
5-HT_{2C} antagonism	Positive symptom alleviation, weight gain
α_1-adrenoceptor antagonism	Sedation, hypotension, weight gain
H_1-histamine antagonism	Sedation, weight gain
M_1-muscarinic antagonism	Memory impairment, gastrointestinal symptoms, dry mouth, blurry vision, less EPS
Mixed 5-HT/NE reuptake inhibition	Antidepressant and anxiolytic activity, less weight gain

5-HT, serotonin; D, dopamine; EPS, extrapyramidal symptoms; NE, norepinephrine.

1. Casey DE, Zorn SH. *J Clin Psychiatry*. 2001;62 Suppl 7:4-10.

Management of Acute Agitation

- The primary goal of intervention is to secure safety of the patient, staff, and other patients. This can be achieved by[1,2]:

Environmental and organizational management	• Implementation of protocols and routines • Removal of any object that may be used as a weapon • Removal of potentially disturbing people
Behavioral and attitudinal management	• Avoid abrupt movements and remain at a safe distance • Speak in a confident, calm, and authoritative tone • Reassure the patient and ask clear, direct questions
Pharmacological management	• Perform a clinical assessment of psychomotor agitation • Although oral treatment is preferred, parenteral administration of drugs is an option • In case additional medication is required, repeat the drug/dose used previously, as appropriate, or add a benzodiazepine
Physical management	• Mechanical restraint should be used as a last resort* • Mechanical restraint should used as little as possible* • Vital signs should be strictly monitored

*Mechanical restraint is forbidden in some countries.

1. Montovani et al. *Revista Brasileira de Psiquiatria*. 2010;32(Suppl II):S96–103;.
2. Mohr et al. *Neuro Endocrinol Lett*. 2005;26:327–335. .

Best Practices in Treating Agitation Due to a Psychiatric Illness*

- Nonpharmacological approaches should be attempted if possible, before medications are administered
- The use of medication as a restraint should be discouraged
- If/when pharmacological intervention is required:
  - For psychosis-driven agitation, antipsychotics are preferred over benzodiazepines because they may address the underlying psychosis
  - SGAs with supportive data for their use in acute agitation are preferred
  - If an initial dose of antipsychotic is insufficient to control agitation, the addition of a benzodiazepine is preferred to additional doses of the same antipsychotic or to a second antipsychotic

*Consensus statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup.
SGA, second-generation antipsychotic.
1. Wilson MP et al. *Western J Emerg Med*. 2012;13:26-34.

Potential Consequences of Long-term Sedation

- Impairment in normal functioning in vocational, academic, social and recreational activities
- Weight gain and other metabolic risk factors
- Impaired cognitive and motor performance
- Increased risk of falls
- Stigma

1. Kane JM et al. *J Clin Psychiatry*. 2008;69 (suppl1 1):18-31.

Case Presentation Revisited

- William is a 37-year old male who was found directing traffic in response to the instructions of a superior being
- Became agitated and violent when police approached
- Taken to emergency department, where he was very agitated and responding to internal stimuli and combative toward staff
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Has your initial treatment consideration changed?

Summary

- During treatment for acute agitation, sedation may hinder diagnosis and may be mistaken for negative symptoms or cognitive defects
- Sedative effects of an antipsychotic may be considered beneficial or unwanted, depending on the clinical setting
- Sedation may not always be needed to reduce symptoms of agitation
- Pharmacologic considerations when selecting an antipsychotic should include its long-term propensity for sedation

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