PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #397
Non-antipsychotics/Non-benzodiazepines in the Management of Agitated Delirium
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Background Although their use remains commonplace, there is not strong evidence to support the use of antipsychotics or benzodiazepines in the management of delirium (1-3). There are also barriers to the use of antipsychotics and/or benzodiazepines in long-term care facilities. While prevention remains key in reducing morbidity from delirium, and nonpharmacologic interventions are the first-line treatments for active delirium, some patients will have distressing and potentially harmful manifestations of delirium such as severe agitation. This *Fast Fact* will discuss the use of non-antipsychotics & non-benzodiazepines in the management of agitated delirium. Much of the discussion is targeted to hospitalized adult patients, because what few data exist have all emerged from this population. It is important to note that there is currently no consensus about the role of any drug to treat delirium (outside of patients near the end-of-life, when sedation is acceptable) including the drugs mentioned here.

Valproate (VPA)
Rationale: VPA was developed as an anticonvulsant. It is used in bipolar disease and acute mania (4). It affects dopamine, GABA and glutamate neurotransmission, all of which are implicated in the pathogenesis of delirium (5).
Evidence: There is low-quality evidence, from case series and retrospective reviews, that VPA reduces agitation in delirious patients in addition to conventional treatments (6-8). No studies compare VPA with placebo in the management of agitated delirium. The median dose reported in an ICU cohort was 1500 mg/d (8).
Practical issues: The starting dose in descriptive studies is between 500 mg to 1500 mg PO/IV a day in two to three doses. The dose is increased according to the patient's response and tolerance usually by 250-500 mg/day every 1-3 days. Unlike with most antipsychotics, VPA can easily be administered intravenously, does not prolong the QT interval, or aggravate parkinsonian symptoms (5). It is available as oral sprinkles for patients with significant pill dysphagia.

Melatonin Receptor Agonists (Melatonin and Ramelteon): see *Fast Fact* #306
Rationale: Melatonin regulates the sleep-wake cycle. Increasing levels of melatonin at dark facilitate sleep initiation and sleep maintenance (9). Low levels of melatonin and lack of melatonin rhythmicity are associated with delirium (10).
Evidence: There is low-quality evidence, from retrospective studies and case series, suggesting the efficacy of melatonin and ramelteon in the management of established delirium (11-13). No randomized controlled trial (RCT) evaluates the use of melatonin and ramelteon with placebo in the management of delirium. Some authors support the use of melatonin receptor agonists to *prevent* delirium (9), however, systematic reviews and meta-analysis of RCTs have not shown consistent benefit (10,14,15).
Practical issues: Although there is limited supporting evidence, melatonin receptor agonists can be considered in agitated delirium patients when there is a circadian rhythm disturbance (16). Melatonin 0.5, 2, 5, 6, 10 mg at bedtime were prescribed in the cases reported (11,12,16). Ramelteon is a synthetic analog of melatonin that has a longer half-life and a higher affinity for melatonin receptors. The studied ramelteon dose is 8 mg at bedtime. Side effects have not been reported for either agent (10).

Dexmedetomidine (DXM): see *Fast Fact* #280.
Rationale: DXM is an alpha-2 adrenergic receptor agonist used as a sedative in ICU patients on mechanical ventilation. It does not affect the respiratory drive or arousal state. DXM decreases the need for gamma-aminobutyric acid (GABA) agents, benzodiazepines, and opioids that are associated with delirium (17).
Evidence: Studies of delirium *prevention* in the ICU setting support this use of DXM (14). In one well-designed, randomized, double-blinded, placebo-controlled study (18), DXM demonstrated efficacy to *treat* delirium in intubated patients, reducing the time to extubation compared to placebo.
Practical issues: Main side effects are hypotension and bradycardia. It has a modest analgesic effect. DXM is expensive, and its use is typically restricted to the ICU.

Clonidine
Rationale: It has similar properties than DXM but lower alpha-2 adrenergic selectivity.
Evidence: A pilot study suggested the role of clonidine infusion in reducing the severity of delirium during the weaning period after surgery for type A aortic dissection (19). A well-designed, double-blind RCT comparing enteral clonidine against placebo in delirious, hospitalized older patients did not demonstrate any benefit, although the trial failed to recruit adequate subjects and was under-powered (21).
Practical issues: Clonidine has analgesic properties, which can be advantageous at times. Abrupt cessation of clonidine causes rebound hypertension (22).

Cholinesterase inhibitors: see *Fast Fact* #174
Rationale: A deficit of acetylcholine is associated with delirium. Cholinesterase inhibitors used in Alzheimer's disease (e.g., donepezil, galantamine) increase the availability of acetylcholine (23).
Evidence: Cholinergic agents such as physostigmine, galantamine, and donepezil are used to treat delirium from anticholinergic poisoning (23). A systematic review of seven RCTs that evaluated the role of cholinesterase inhibitors (rivastigmine and donepezil) in the treatment or prevention of delirium in older adults, did not find any meaningful benefit (24).
Practical issues: Nausea, vomiting, and diarrhea are common side effects for this medication class.

Summary Of the above-mentioned drugs, only DXM has high quality evidence supporting its use, albeit in a narrow population (agitated patients on ventilators). Other drug classes need additional research before their clinical applicability is understood.

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