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Identifying and Managing Psychiatric Emergencies

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Most U.S. medical schools require only five core clinical rotations in the third year – internal medicine, surgery, pediatrics, obstetrics and gynecology, and psychiatry. Despite the growing number of medical-surgical subspecialties, there are fundamental reasons that psychiatry remains a core clinical requirement for medical school graduation and physician training: psychiatric disease is highly prevalent, extremely distressing to patients and families, associated with high levels of disability and health care costs, linked to significant reductions in quality of life, and has adverse effects upon the course of many illnesses with which it is co-morbid, including diabetes mellitus, cardiovascular disease, and stroke, amongst others.

Despite great advances in the understanding of the neurobiological underpinnings of psychiatric disease and the development of more effective and better tolerated medications, patients with severe and persistent mental illness (SPMI) such as schizophrenia and bipolar disorder have a life expectancy that is 15-20 years shorter than that of the general population. This reduction in life expectancy is due not only to suicide but to co-morbid substance abuse and the more aggressive course of associated medical illnesses driven by suboptimal adherence with care, inadequate attention to modifiable risk factors for disease, metabolic side effects of psychotropic medications, and other still poorly understood psychophysiologic mechanisms that affect other organ systems.

Psychiatry as a specialty has its roots in neurology. Their theoretical, diagnostic, and therapeutic paths, however, diverged through much of the 20th Century. After years of treating psychiatric and neurologic disease separately, the pendulum has swung and the specialties find themselves comfortably and appropriately reconnected. Perhaps better considered as *neuropsychiatry*, today's psychiatry is poised at the interface of medicine and neurology and seeks to understand the brain basis of behavior, the neurologic roots of psychiatric disease, the behavioral presentations of neurologic disease, and the psychosomatic and psychophysiologic relationships between medical and psychiatric illness.

No less important to a *newer* neuropsychiatric conceptualization of mental illness is a *renewed* emphasis on the fundamental and traditional bio-psycho-social factors that inform the presentation and course of medical and psychiatric disease – such as access to care, employment status, community supports, interpersonal relationships, family function, and specific personality factors.

This issue of the *Rhode Island Medical Journal* (RIMJ) is dedicated to a discussion of psychiatric emergencies and frequently encountered urgent behavioral problems. It includes articles on delirium diagnosis and treatment, management of neuropsychiatric symptoms in dementia, recognition and treatment of serotonin syndrome, toxidromes related to newer designer drugs, and practical approaches to the management of the behaviorally dysregulated "problem patient."

CONTRIBUTIONS

- In "Delirium Diagnosis and Treatment: Parts I and II," I have joined with my co-author, **KALYA VARDI, MD**, to review the presentation, causes, pathophysiology, evaluation, and treatment of delirium. Delirium is highly prevalent and is associated with multiple adverse patient and systems outcomes. It is often under-recognized and can be difficult to treat. Behavioral and pharmacologic treatments and preventative strategies are discussed.
- In "The 'Problem Patient': Modest Advice for Frustrated Clinicians," **ROBERT BOLAND, MD**, provides a discussion of personality constructs and abnormal illness behaviors that often interfere with the effective and efficient delivery of care. These patients and behaviors can challenge even the most even-tempered of physicians, nurses, and hospital staff. Dr. Boland discusses issues of countertransference and offers practical suggestions regarding staff approach to these patients – with the specific goals of optimizing patient engagement in care and avoiding responses that can escalate behavioral dysregulation.
- "Serotonin Syndrome: A Concise Review of a Toxic State" by **DWAYNE HEITMILLER, MD**, focuses on the presentation, implicated drugs, pathophysiology, and management of this iatrogenic toxidrome. Differential diagnosis, including neuroleptic malignant syndrome, and preventative strategies are emphasized.
- In "Practical Management of Alzheimer's Dementia," authors **JEFFREY BUROCK, MD**, and **LILLY NAQVI, BS**, review molecular mechanisms operative in Alzheimer's disease and newly developed anti-amyloid therapies, and focus on the treatment of cognitive dysfunction and neurobehavioral symptoms in dementia.

- **ELIE AOUN, MD**, **PAUL CHRISTOPHER, MD**, and **JAMES INGRAHAM, MD**, in "Emerging Drugs of Abuse: Clinical and Legal Considerations," focus on the clinical presentations, recognition, and management of novel toxidromes associated with newer illicit drugs. Neurotransmitter mechanisms operative in these intoxication states are reviewed. Emergency departments and psychiatric services in Rhode Island and nationally have seen a remarkable rise in these complicated, severe, and sometimes lethal syndromes.

Why are these subjects treated together in this issue of RIMJ? These illness and clinical problems are prevalent, tax our health care system, and cut across medical specialties. To effectively address and manage diagnoses like dementia, delirium, toxidromes, substance abuse, and health-rejecting patients, physicians must work collaboratively, bringing their various areas of expertise to bear on complex clinical presentations. Health care reform has only hastened the increasing interest in collaborative care, with an eye towards psychiatry's role in an integrated system to improve outcomes and reduce health care costs. The reader is encouraged to consider these diagnoses in the context of an integrated model of health care delivery.

Guest Editors

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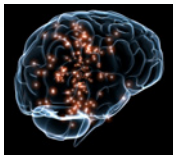

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Delirium: Presentation, Epidemiology, and Diagnostic Evaluation (Part 1)

COLIN J. HARRINGTON, MD; KALYA VARDI, MD

ABSTRACT

Delirium is a highly prevalent and complex neuropsychiatric disorder marked by attentional dysfunction, disturbances in multiple cognitive domains, and changes in motor behavior, perception, sleep, and thought process. Delirium results from diverse toxic, metabolic, infectious, and structural etiologies and is associated with a number of adverse outcomes. Delirium pathophysiology involves perturbation of multiple neurotransmitter systems. Behavioral presentations of delirium are common and are often misattributed to primary psychiatric processes. Diagnostic assessment of delirium includes thorough physical examination, careful cognitive testing, appropriate metabolic and infectious studies, review of medications, and structural brain imaging and electroencephalography as indicated. Pharmacologic and non-pharmacologic interventions have been documented to reduce the incidence and severity of delirium. Antipsychotics are the treatment of choice for delirium-related agitation and psychosis.

KEYWORDS: Delirium, encephalopathy, cognitive disorder, agitation

INTRODUCTION

Delirium is a complex neuropsychiatric disorder marked by an alteration in level of consciousness, attentional dysfunction, disturbances in other cognitive domains including memory, orientation, and language, and associated changes in non-cognitive domains of motor behavior, perception, affect, sleep-wake cycle, and thought process.[1,2] Delirium results from diverse etiologies and is associated with a number of adverse clinical and systems outcomes including secondary infections, falls, violence, and increased hospital length-of-stay, healthcare costs, and mortality.[1-8] While the pathophysiology of delirium is poorly understood, the neurobehavioral syndrome likely represents a final common pathway of perturbation of multiple neurotransmitter systems operative across widely distributed neural networks.[1,9-11]

At its core delirium is a cognitive disorder and, as such, associated neurobehavioral changes and psychiatric signs and symptoms are considered *secondary*. Delirium has been described in the medical literature since antiquity and has acquired many diagnostic labels including acute confusional state, acute brain dysfunction, acute brain failure, acute organic brain syndrome, ICU psychosis, and metabolic encephalopathy, amongst others. The term *delirium* is derived from the Latin roots *de* (translated "away from") and *lira* (translated "furrow of a field") thus suggesting that one is derailed from the plowed or straight path.[11]

The term *encephalopathy* is often employed in place of or alongside delirium and allows for the proper grouping together of delirium and dementia as cognitive disorders – while also providing for the longitudinal course-based distinction between delirium and dementia, as acute and reversible, and chronic and progressive forms of encephalopathy, respectively. Use of this terminology also allows for description of the intermediate syndrome of sub-acute encephalopathy where cognitive dysfunction is often less obvious and neuropsychiatric symptoms predominate.

EPIDEMIOLOGY, RISK FACTORS, AND OUTCOMES

Delirium is a highly prevalent disorder estimated to occur in 10%-15% of general medical-surgical inpatients, in 25%-45% of hospitalized cancer patients, and in 80%-90% of terminally ill palliative care patients.[1,4,5,11,12] Rates of delirium are particularly high in the intensive care unit (ICU) where studies suggest that 30% of patients are delirious on admission and 60% develop delirium during the course of their critical illness.[1,3,5,13-15] Upwards of 80% of mechanically ventilated ICU patients are estimated to be delirious.[14-16]

Models of delirium etiology suggest predisposing, precipitating, and perpetuating factors.[1,2,4,11,17] Illness, pharmacologic, and environmental factors likely play roles in the development and persistence of delirium. Identification of modifiable factors is crucial to prevention and optimal management of delirium. Older age, premorbid cognitive dysfunction, medical illness burden, baseline poor functional status, and medication exposure are most highly predictive of delirium development.[1,2,4,5,11] Baseline cognitive dysfunction is the most robust predictor of incident delirium in the hospitalized patient with upwards of 60% of acute encephalopathy episodes thought to occur atop a baseline of cognitive impairment.[1,13,17,18] Delirium superimposed on dementia or other types of cognitive dysfunction appears more resistant to treatment.[1,19] Surgical patients, especially those undergoing total joint replacement and cardiac procedures requiring bypass, are at particularly high risk for the development of delirium.[4,20-22]

Delirium is associated with numerous adverse outcomes including prolonged hospital length of stay,[1] increased rates of discharge to institutional care settings,[3] increased healthcare costs,[8] reduced quality of life,[1,11] increased short- and long-term mortality,[5-7] and long-term cognitive impairment.[9,13,14,18] Delirium in the ICU, after controlling for numerous confounders, is associated with an increase in ventilator dependent days and ICU length of stay, and is an independent predictor of increased mortality in mechanically ventilated patients.[16] Delays in diagnosis and treatment of delirium are associated with increased mortality in ICU patients.[23]

CLINICAL PRESENTATION, EXAMINATION, AND COURSE

There are many definitions of delirium in the literature. Factor analysis studies suggest that the broad and heterogeneous phenotype of delirium loads onto three core symptom domains including a "cognitive" domain (orientation, attention, short-term memory, long-term memory, and visuospatial ability), a "higher level thinking" domain (language and thought process), and a "circadian" domain (sleep-wake cycle and motor behavior).[24] Common to all definitions of delirium is a disruption in attention, often signaled by a frank alteration in level of consciousness or sensorium. On a spectrum between stupor and normal consciousness, delirium presentations can range from frank somnolence to more awake and alert states marked by subtle concentrational difficulty.[1] Intact attentional *function* includes the ability to focus, maintain, and shift attention according to environmental demands. Attentional *dysfunction* may manifest in clinical findings of obvious confusion with incongruent responses to the examiner's queries and in more subtle ways where patients can focus initially but are distractible, impersistent, or perseverative on bedside and formal neurocognitive testing. If basic attention and concentration are impaired, then more complex cognitive functions of language, orientation, memory, and thought process are secondarily disturbed. In cases of severe delirium, attentional impairment can frankly preclude adequate assessment of other higher order cognitive domains.

When attention and awareness are altered, the delirious patient's navigation of the environment is impaired. The surgical dictum to "look, listen, and feel" regarding the examination of the acute abdomen is applicable to the examination of the delirious patient as well. Observation of patients from a distance can provide clues about their cognitive function. Disheveled appearance, restless fidgeting, picking behavior, and talking out loud when alone in the room suggest inattention to self, disconnection from the environment, and response to internal stimuli. Just as palpation of the abdomen can alter the findings of auscultation, so too can more formal examination of delirious patients alter their cognitive performance. When engaged with a more structured cognitive assessment, the confused patient can sometimes "borrow the frontal lobe" of the organized examiner and respond more appropriately than expected – a particularly relevant issue in the assessment of the less obviously encephalopathic patient where proper diagnosis of abnormal behavior hinges on a comprehensive neuropsychiatric assessment. In this regard, the act of examining the patient may change the examined – and thus should come after a period of simple observation and casual engagement.

Delirium typically develops over hours to days. Subacute encephalopathies due to smoldering infection, slowly developing metabolic derangements, chronic lithium intoxication, and other drug toxicities can evolve over days to weeks. Cognitive and behavioral changes frequently fluctuate and follow a diurnal pattern. Assessment during periods of more lucid behavior can lead to the conclusion that patients are cognitively intact, making subsequent behavioral changes and agitation diagnostically difficult to understand.

Changes in motor behavior are common in delirium. Hypoactive and hyperactive subtypes of delirium have been identified. Different pathophysiologies have been proposed for the two motor subtypes but have not been supported to date. Patients often fluctuate between these two forms of delirium making single cross-sectional assessment diagnostically insufficient. Hyperactive delirium, often the result of drug intoxication and withdrawal states, can be associated with agitation and related patient and staff injury. Some studies suggest prognostic relevance to the motor subtypes, with hyperactive delirium more responsive to pharmacologic treatment and hypoactive delirium predictive of worse outcome.[1,2,11]

Psychiatric symptoms and neurobehavioral changes are common in delirium and range from frank agitation, to restlessness, anxiety, dysphoria, tearfulness, apathy, withdrawal, disinhibition, disordered thinking, and perceptual disturbances of hallucinations and delusions. In contrast to behavioral symptoms of *primary* psychiatric syndromes that occur in a clear sensorium, behavioral changes in delirium occur atop a substrate of clinically demonstrable abnormal brain function and are properly considered *secondary* phenomena. New onset psychiatric symptoms should trigger examination of cognitive *function* and evaluation for causes of cognitive *dysfunction* when it is demonstrated, especially in the elderly and medically ill.

Despite its high prevalence and associated morbidity and mortality, delirium often goes undetected. Behavioral changes of delirium are commonly attributed to primary psychiatric processes, leading to delays in diagnosis and treatment of its causes.[1,15,19,23] Hypoactive delirium is often mistaken for depression – where psychomotor slowing, poor oral intake, and limited engagement with family and staff are attributed to vegetative dysfunction and psychological withdrawal of a mood disorder. Restlessness and anxiety in the medically ill patient are often considered appropriate psychological responses to the illness experience (rather than symptoms

of delirium). Failure to cognitively probe these behavioral changes and to recognize them as manifestations of delirium often leads to delays in diagnosis of the causative medical-surgical illness, the introduction of unnecessary antidepressant medications, and the initiation of potentially deliriogenic benzodiazepines.

Hallucinations, illusions, and delusional ideation, typically paranoid, are particularly common in delirium and are highly distressing to patients, families, and staff.[12,25,26] These misperception symptoms result from cognitive misprocessing that leads to misinterpretation of sensory phenomena and misattribution of meaning to routine hospital events. Patients often report that they are being poisoned, experimented on, plotted against, or held captive (note, many *are* physically restrained and treated with injectable medications). Psychiatric consultation for a question of "psychosis" is often requested in these cases. Onset of primary psychosis in the elderly and medically ill is extremely unusual and new hallucinations or delusions in this population should be considered diagnostic of delirium or dementia until proven otherwise.

While considered a transient syndrome and indicative of typically reversible processes, recent data suggest that many delirium episodes last longer than initially presumed. As many as 30%-40% of patients discharged to nursing homes and skilled nursing facilities remain delirious at the time of transfer.[1] Delirium is a risk factor for long-term cognitive impairment, especially in survivors of critical illness and in cases of sepsis-related encephalopathy.[3,9,13,14,18,27]

RISK FACTORS AND CAUSES

Delirium is caused by a wide variety of etiologies including metabolic, toxic-pharmacologic, infectious, vascular, traumatic, and post-surgical conditions.[1,11,24] Though the vast majority of delirium episodes are not caused by structural disease, brain imaging is performed in most delirious patients as part of the initial evaluation. Structural causes of delirium are typically heralded by a history of trauma or a focal neurological exam. Delirium often evolves in hospitalized stroke patients and is typically the result of metabolic and infectious complications. Stroke as a direct cause of delirium is less common.

The pathophysiology of delirium is poorly understood. Inflammatory mechanisms are active in infectious, metabolic, traumatic, and other processes linked to delirium. Animal and human studies have documented numerous adverse mood, cognitive, and behavioral effects of various inflammatory mediators including interferon-alpha, interleukin-1, interleukin-6, and tumor necrosis factor-alpha. Illness-related *systemic* inflammation is thought to play a central role in delirium etiology of multiple causes.[28,29]

Dysfunction of various neurotransmitter systems has been implicated in the pathophysiology of delirium. Derangement of dopaminergic and serotonergic neurotransmitter function is likely causative in diagnoses of neuroleptic malignant

Table 1. Selected causes of delirium

Autoimmune	**Metabolic**
Acute graft versus host disease	Acidosis or alkalosis
Autoimmune encephalopathy (voltage-gated potassium channel, NMDA receptor)	Anemia
Central nervous system vasculitis	Hepatic failure
Hashimoto's encephalopathy	Hypercapnea
Systemic lupus erythematosus	Hypoalbuminemia
Cardiac	Hypo- or hypercalcemia
Acute myocardial infarction	Hypo- or hyperglycemia
Heart failure	Hypo- or hyperkalemia
Cerebrovascular	Hypo- or hypermagnesemia
Stroke (ischemic, hemorrhagic)	Hypo- or hypernatremia
Transient ischemic attack	Hypophosphatemia
Subarachnoid hemorrhage	Hypoxemia
Hypertensive encephalopathy	Uremia
Drug intoxication	Other (carcinoid, porphyria, etc)
Alcohol	**Neoplastic**
Bath salts	Carcinomatous meningitis
Cannabinoids (marijuana, synthetic)	Intraparenchymal brain tumor
Gamma-hydroxybutyrate	Lymphomatous meningitis
Hallucinogens	Parenchymal metastasis
Opiates	Paraneoplastic syndrome
Psychostimulants	**Systemic infection**
Sedative-hypnotics (benzodiazepines, barbiturates)	Bacteremia
Drug withdrawal	Cellulitis
Alcohol	Pneumonia
Sedative-hypnotics (benzodiazepines, barbiturates)	Sepsis
Endocrine	Urinary tract infection
Adrenal insufficiency or excess	**Traumatic brain injury**
Hypo- or hyperthyroidism	Diffuse axonal injury
Hypo- or hyperparathyroidism	Parenchymal contusion
Panhypopituitarism	Subdural hematoma
Intracranial infection	**Other**
Abscess	Central nervous system radiation
Encephalitis (HSV, arboviruses)	Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura
Human immunodeficiency virus	Malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome
Meningitis (bacterial, viral, fungal)	Postoperative state (cardiotomy, joint arthroplasty)
Neurosyphilis	Seizures

*See Table 2 for drugs causing delirium

Adapted from:Trzepacz PT, Meagher DJ, and Leonard M. (2011). Delirium. In Levenson JL (Ed), *Textbook of Psychosomatic Medicine*. Arlington, VA: American Psychiatric Publishing, Inc.

syndrome and serotonin syndrome, respectively. Deficient gamma-aminobutyric acid (GABA) function and glutamate hyperactivity have been implicated in the encephalopathy of sedative-hypnotic withdrawal. The anti-cholinergic properties of numerous medications (**Table 2**) play a role in the development of delirium. Opiate narcotics drive delirium via both their opioid and anti-cholinergic effects.

Causes of delirium cut across all organ systems. Derangements in sodium and calcium metabolism, hypoalbuminemia, hypoxemia, hypercapnea, hepatic and renal insufficiency, hyper and hypoglycemia, drug intoxication and withdrawal, infection, and primary central nervous system diseases including stroke, seizure, and traumatic brain injury have all been associated with delirium.[1,11] (**Table 1**).

Medications from multiple classes, via both well-understood and more idiosyncratic mechanisms, have been associated with delirium (**Table 2**). Antimicrobials (antiviral acyclovir, macrolide antibiotics including clarithromycin, fluoroquinolones such as ciprofloxacin, penicillins, cephalosporins, and metronidazole), anticonvulsants (phenytoin, phenobarbital, valproic acid), corticosteroids, antiparkinson agents (amantadine, levodopa), cardiac drugs (digitalis, lidocaine, quinidine, and beta-blockers), and various antineoplastic agents (5-fluoruracil, methotrexate, procarbazine, vincristine, interferon alpha, and ifosfamide) have all been implicated in the development of delirium. Opioid analgesics and benzodiazepines are especially common causes of delirium in hospitalized medical-surgical patients.

Acute *intoxication* with virtually any abuseable prescription or illicit drug can drive a delirium. Drug *withdrawal* delirium, however, is more specifically associated with use of sedative-hypnotic agents (i.e., alcohol, benzodiazepines, and barbiturates) that share a GABA-ergic mechanism of action and drive a delirium tremens-like encephalopathy syndrome. While there are case reports of delirium associated with abrupt discontinuation of opioid narcotics (methadone), these agents typically do not produce a withdrawal delirium. Presumption of opioid withdrawal as the cause of delirium in opioid abusers or medical-surgical patients exposed to prolonged courses of narcotic analgesics is ill advised as these patients are often affected by and at risk for multiple delirium-related conditions.

Emergency department presentations for acute mental status change are extremely common and have given rise to protocol driven empiric treatment of frequently occurring reversible causes of delirium. Emergency protocols, in parallel with appropriate diagnostic testing, include the administration of supplemental oxygen, intravenous dextrose, intravenous normal saline, naloxone, and thiamine targeting, respectively, hypoxemia, hypoglycemia, hypovolemia, opioid intoxication, and Wernicke's encephalopathy. Flumazenil, a benzodiazepine reverse agonist, is sometimes administered for suspected benzodiazepine intoxication, but reports of benzodiazepine withdrawal-induced seizures have led to more cautious use of this agent.

Table 2. Selected drugs causing delirium

Analgesics	**Antiparkinsonian drugs**
Opiates	Amantadine
Salicylates	Bromocriptine
Antimicrobials	Dopamine agonists
Acyclovir, gancyclovir	(ropinirole, pramipexole)
Aminoglycosides	Levodopa
Amphotericin B	**Cardiac drugs**
Antimalarials	Beta-blockers
Cephalosporins	Captopril
Ethambutol	Clonidine
Interferon	Digoxin
Isoniazid	Lidocaine
Macrolides (clarithromycin)	Methyldopa
Metronidazole	Procainamide
Quinolones (ciprofloxacin)	Quinidine
Rifampin	Tocainide
Sulfonamides	**Sedative-hypnotics**
Vancomycin	(intoxication or withdrawal)
Anticholinergic	Barbiturates
Antihistamines (H_1)	Benzodiazepines
Antispasmodics	**Stimulants**
Atropine and atropine-like drugs	Amphetamines
Benztropine	Epinephrine, phenylephrine
Phenothiazines	Pseudoephedrine
Tricyclics (amitriptyline, doxepin, imipramine)	Theophylline
Trihexiphenidyl	**Miscellaneous**
Anticonvulsants	Antihistamines (H_2)
Phenobarbital	Baclofen (intoxication or withdrawal)
Phenytoin	Bromides
Valproic Acid	Disulfiram
Anti-inflammatory drugs	Ergotamine
Corticosteroids	Lithium
Nonsteroidal anti-inflammatory drugs	Propylthiouracil
Antineoplastic drugs	Quinacrine
Asparaginase	Timolol (ophthalmic)
Dacarbazine	
Diphosphamide	
5-Fluorouracil	
Methotrexate	
Procarbazine	
Vinblastine	
Vincristine	

Adapted from: Trzepacz PT, Meagher DJ, and Leonard M. (2011). Delirium. In Levenson JL (Ed), *Textbook of Psychosomatic Medicine*. Arlington, VA: American Psychiatric Publishing, Inc.

EVALUATION

Delirium evaluation begins with a thorough physical examination with particular attention paid to findings suggestive of metabolic derangement, infection, and neurologic focality. Routine metabolic studies should be checked and urinalysis and chest X-ray obtained. Brain imaging is often performed in the assessment of delirium, but is typically unrevealing. Brain computed tomography (CT) scanning is indicated for evaluation of intraparenchymal or subdural hemorrhage in patients with a history of trauma or focal neurologic examination findings. Magnetic resonance imaging (MRI) is more sensitive in evaluating for space occupying lesions, white matter disease processes, and new ischemic stroke as causes of delirium.

Electroencephalography (EEG) in delirium typically reveals diffuse bilateral background slowing in the delta to theta range. These EEG changes are non-specific and common to encephalopathies of diverse etiologies. Certain causes of delirium are associated with specific EEG findings including triphasic waves in hepatic encephalopathy, excess beta-range activity in benzodiazepine intoxication, and periodic discharges and burst suppression in prion diseases.

EEG is not particularly helpful when neuropsychiatric assessment is consistent with a diagnosis of delirium and physical examination and laboratory investigation suggest its cause(s). In contrast, even non-specific background slowing on EEG can be very helpful in distinguishing between abnormal behavior of psychiatric disease and that of more subtle, subacute encephalopathy where cognitive dysfunction is *less obvious* – as the EEG in most psychiatric disorders is normal.

When patients are *obviously* encephalopathic but evaluation for toxic, metabolic, infectious, and structural causes is unrevealing, EEG is indicated to evaluate for non-convulsive status epilepticus (NCSE). Recent studies have documented unexpectedly high rates of NCSE in critically ill and ICU patients.[30] This is a notable finding that argues for more liberal use of EEGs in encephalopathic critically ill patients who typically have multiple non-epileptic processes driving their delirium and in whom EEG has previously been thought to be less indicated.

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Delirium: Treatment and Prevention (Part 2)

KALYA VARDI, MD; COLIN J. HARRINGTON, MD

ABSTRACT

Delirium management begins with non-pharmacologic interventions and treatment of the underlying causes. There are no FDA-approved medications for delirium-related psychosis and agitation, although numerous agents have been studied. Small sample size, narrow inclusion criteria, lack of placebo controls and variable methodologies limit the generalizability of findings to date. Studies and expert guidelines support the use of antipsychotics for delirium-related psychosis and agitation, and demonstrate comparable efficacy and safety between first- and second-generation agents. Mounting evidence also suggests that antipsychotics and dexmedetomidine are effective in preventing delirium in surgical and mechanically-ventilated patients, respectively.

KEYWORDS: delirium, encephalopathy, cognitive disorder, agitation

INTRODUCTION

Delirium management begins with evaluation and treatment of its causes, discontinuation of potential offending agents, and institution of non-pharmacologic strategies to limit its incidence, course and complications. Pharmacologic treatment is typically reserved for neurobehavioral symptoms of agitation and psychosis that are unresponsive to these primary interventions. Despite its high prevalence and association with multiple adverse outcomes, there are no FDA-approved treatments for delirium.

Studies of delirium management have explored both treatment and prevention, have been conducted in general medical-surgical patients and in critically ill, intensive care unit (ICU) populations, and have included both pharmacologic and non-pharmacologic interventions. Unfortunately, small sample size, narrow inclusion criteria, lack of placebo controls, and variable methodologies limit the generalizability of findings to date.

Numerous agents have been studied for delirium management including antipsychotics, benzodiazepines, cholinesterase inhibitors and other pro-cholinergic drugs, ketamine, and, more recently, dexmedetomidine. Published guidelines from numerous subspecialty societies and recent meta-analyses recommend haloperidol and other antipsychotic agents for the treatment of delirium.[1,2] Based on these and other consensus statements, antipsychotic agents remain the treatment of choice for delirium and related agitation.

NON-PHARMACOLOGIC INTERVENTIONS

The landmark study by Inouye et al tested a multi-disciplinary protocol of non-pharmacologic interventions to reduce delirium incidence, duration and severity in 852 elderly patients admitted to the general medical service of an academic hospital.[3] The protocol consisted of both global interventions and targeted interventions for patients with specific risk factors. Interventions included early mobilization, noise reduction and scheduling adjustments to minimize sleep disruption, early recognition and treatment of dehydration, orientation boards and frequent verbal reorientation for patients with cognitive impairment, and communication aids for patients with visual and hearing impairment. The incidence of delirium was 40% lower in the intervention group compared with the control group. The total number of days spent in delirium was also significantly lower in the intervention group. Zaubler et al replicated these results and reported $841,000 in cost savings over 9 months in a community hospital setting.[4] These protocols are considered the standard of care and have been put in place at institutions across the country. Similar non-pharmacologic interventions have been designed and implemented by the Brown-based Geriatric Medicine Program, and form the basis of the Close Observation Medical Unit (COMU) and other elder-care protocols at Rhode Island Hospital and The Miriam Hospital, respectively (L. McNicoll, personal communication, July 2012).

PHARMACOLOGIC INTERVENTIONS – TREATMENT AND PREVENTION

Overview

First generation antipsychotics (FGA), such as haloperidol, are the mainstay for treating the neurobehavioral symptoms of delirium.[1,5,6] Their utility is thought to derive from dopaminergic blockade, based on the hypothesis that dopaminergic hyperactivity and cholinergic deficiency contribute to the onset and persistence of delirium. For this reason, cholinesterase inhibitors have also been tried with mixed results.[6] Haloperidol has minimal hemodynamic side effects and

remains the best studied and most recommended treatment for delirium-related agitation. Haloperidol can be administered orally, intramuscularly (IM) or intravenously (IV), has a wide therapeutic window, and can be titrated across a broad dose range, from 0.5 mg as needed to 10 mg hourly, with onset of action between 30-60 minutes for the IV and IM routes of administration. Peak serum concentrations occur 2-6 hours after oral administration. There are case reports of safe and effective haloperidol administration up to 500 mg per day.[5] Intravenous and IM forms of haloperidol are particularly helpful in uncooperative patients and in critically ill patients where gastrointestinal absorption is unreliable. Numerous reports suggest that IV administration is associated with less risk of extrapyramidal symptoms (EPS).[5] Emerging data suggests that, in addition to its anti-dopaminergic action, haloperidol may also counter delirium by decreasing oxidative stress and inflammation via σ-1 receptor blockade and interleukin-1 antagonism.[6]

There is a literature supporting the use of second-generation antipsychotics (SGAs) in the treatment of delirium-related agitation and psychosis.[2,5-9] SGAs studied to date include risperidone,[10,11] quetiapine,[12] olanzapine,[9,13] ziprasidone,[5] and aripiprazole.[5] The main advantage of the SGAs over haloperidol is their relatively reduced risk of EPS, which is particularly relevant in patients with parkinsonian syndromes such as dementia with Lewy bodies (DLB) and idiopathic Parkinson's disease (PD). Quetiapine is least likely to produce or exacerbate EPS and is the agent of choice in treating agitation and psychosis in parkinsonian patients. Unlike haloperidol, none of the SGAs are available IV. Olanzapine, ziprasidone, and aripiprazole can be administered in immediate-release intramuscular forms and are indicated when the oral route is unavailable and haloperidol is contraindicated. Risperidone and paliperidone are available in long-acting intramuscular depot formulations which are utilized in the treatment of patients with chronic psychotic illnesses, but are not indicated in delirium.

The FDA issued "black box" warnings in April 2005 and June 2008 regarding the use of antipsychotic agents in the elderly. These warning were based upon evidence of increased cerebrovascular events and all-cause mortality in studies of extended courses of antipsychotic treatment in elderly, demented nursing home patients.[14] The relevance of these findings and warnings to the short-term use of these agents in patients with delirium is unclear. Given the high prevalence of co-morbid dementia in delirium patients, these warnings should be taken into consideration when weighing the potential risks and benefits of brief antipsychotic treatment against those of untreated delirium.

Haloperidol and all SGAs carry a risk of QTc prolongation (QTP) and QTP is the best predictor of torsade de pointes (TdP), a malignant ventricular dysrhythmia. The QT prolonging effects of antipsychotic and other agents are catalogued at www.torsades.org. Low-dose oral haloperidol has minimal QT prolonging effects. Thioridazine, ziprasidone and high-dose IV haloperidol have the most significant QT prolonging effects of the antipsychotic agents. Although the degree of QTP and absolute risk of TdP associated with these agents is small, most guidelines advise caution when using IV haloperidol in patients with risk factors for QTP or TdP (**Table 1**). The absolute risk of TdP for IV haloperidol has been estimated at 0.27%.[5]

Table 1. Assessing and Monitoring Risk for Drug-Induced QTc Prolongation (QTP)

Risk Factors for QTP:
• Advanced cardiac disease
• Known history of long-QT syndrome
• Baseline QTc > 450 msec
• Hypokalemia
• Hypomagnesemia
• Concomitant use of other QTc prolonging agents
Prior to Initiating a QTc Prolonging Drug:
• Obtain electrocardiogram to measure baseline QTc interval
• Obtain serum potassium and magnesium levels
• Correct any electrolyte abnormalities
• Review medication list for QTc-related interactions
After Initiating a QTc Prolonging Drug:
• Repeat electrocardiogram at regular intervals (typically once daily)

Dexmedetomidine is a highly selective, centrally-acting alpha-2 agonist with sedative, analgesic and anxiolytic properties, and has been studied for both prevention of delirium and treatment of delirium-related agitation in ICU patients. Trials comparing dexmedetomidine to benzodiazepine and opioid ICU sedation protocols have demonstrated its efficacy, safety and favorable side effect profile.[15-19] Unlike most other sedatives employed in the ICU, dexmedetomidine is not associated with significant respiratory depression; however, hypotension and bradycardia can complicate its use, especially at high infusion rates.[6,15-19] Multiple studies have reported decreased opiate requirements in ICU and post-operative patients sedated with dexmedetomidine.[5] Reduced opioid use likely contributes to the lower incidence of delirium observed in dexmedetomidine-treated patients. Dexmedetomidine is also thought to have mild cholinergic activity which may favorably affect the sleep-wake cycle.[5]

Benzodiazepines are potentially deliriogenic. Except for cases of alcohol and sedative-hypnotic withdrawal where they are the treatment of choice, benzodiazepines are not considered first-line agents in the treatment of delirium-related agitation.[20] *Adjunctive* use of benzodiazepines is appropriate in cases of agitation related to certain toxidromes and neuroleptic-malignant syndrome, or when delirium is complicated by catatonia or severe EPS that limit the use of antipsychotic agents.

The existing literature is summarized below with special attention to differences between *general medical-surgical* patients versus *ICU* patients. Outcome measures vary across these studies and include delirium incidence, severity and duration, length of hospitalization, length of time in the ICU, number of ventilator dependent days, and disposition to home versus other medical facilities or institutional settings.

Typical teaching recommends the use of antipsychotic agents for the treatment of delirium-related psychosis and agitation but not for the delirium syndrome proper. Animal studies suggest that dopaminergic mechanisms play a role in the development of delirium irrespective of the presence or absence of agitated behavior. Additionally, recent studies and personal accounts suggest that a significant proportion of non-agitated, "hypoactive" delirium patients experience distressing psychotic symptoms and that these frightening symptoms may drive the development of a post-traumatic stress disorder (PTSD)-like syndrome.[21,22] Taken together, these observations may argue for more liberal use of dopamine-blocking agents in the treatment of delirium, even in the absence of problem behaviors.

TREATMENT STUDIES

General Medical and Surgical Patients

Multiple case reports and small, open-label trials suggest that SGAs (including risperidone, quetiapine, olanzapine, aripiprazole and ziprasidone) are effective and safe in the treatment of delirium.[5,9-13] Several single-blind, randomized trials comparing SGAs to haloperidol for the treatment of delirium found no significant differences between the two interventions in treatment outcomes or adverse effects.[5] One double-blind RCT of risperidone versus haloperidol in 28 delirious patients reported comparable improvement across groups.[10] A 2007 Cochrane review of antipsychotic use in delirium included a meta-analysis of haloperidol, olanzapine, risperidone and placebo treatment studies, and concluded that (1) haloperidol does not significantly reduce delirium *incidence* compared with placebo, (2) low-dose haloperidol reduces delirium severity and duration in post-operative patients, (3) low-dose haloperidol and the SGAs have similar efficacy and EPS incidence, and (4) higher dose haloperidol is associated with more severe EPS.[8]

ICU Patients

In the MIND study, which evaluated prevention and treatment, 101 mechanically-ventilated ICU patients were randomized to receive oral haloperidol, oral ziprasidone, or placebo for up to 14 days according to a protocol which allowed for dose adjustments based on delirium severity, level of sedation and side effects.[23] Neither agent significantly reduced the duration of delirium, although the study was most likely underpowered due to small sample size, inclusion of patients without delirium at baseline, and open-label IV haloperidol use across groups. There was no difference in duration of coma between groups, a measure included due to concern that the sedating effects of antipsychotics may prolong coma. Rates of EPS, including akathisia, were comparable across groups. Extrapyramidal signs and symptoms were assessed by physical exam. Akathisia in particular, could only be assessed when patients were neither comatose nor delirious, and could participate in the assessment. A 2013 international study used similar methods to compare IV haloperidol to placebo for prevention and treatment of delirium in mechanically-ventilated patients, and found no significant difference between groups in duration of delirium.[24]

Devlin et al randomized 36 delirious, ICU patients to receive oral quetiapine or placebo.[12] Treatment with quetiapine was associated with shorter total duration of delirium, shorter time to first resolution of delirium, and less hours of agitation compared with placebo. Significantly more adverse effects were reported in the quetiapine group, especially sedation; however, no EPS or QTP were observed.

In a small, open-label trial, mechanically-ventilated ICU patients with severe agitation secondary to delirium were randomized to receive a continuous infusion of either dexmedetomidine or haloperidol.[15] The dexmedetomidine group spent more time with minimal or no delirium symptoms, less time intubated, less time in the ICU and less time in mechanical restraints. Three patients receiving haloperidol could not be extubated and underwent tracheostomy, compared with none in the dexmedetomidine group. Haloperidol was discontinued early in one patient due to QTP.

A qualitative meta-analysis of antipsychotic use for delirium in ICU patients reviewed three studies including the MIND and Devlin trials and a study by Skrobik et al of 73 delirious ICU patients randomized to oral olanzapine or haloperidol.[9] Evidence was strongest for the beneficial effects of quetiapine in the treatment of delirium. Guidelines from the American College of Critical Care Medicine (ACCM) report similar evidence for quetiapine and other SGAs in comparison to haloperidol in reducing the duration of delirium in ICU patients.[2,9]

An RCT of rivastigmine versus placebo as adjunct to haloperidol for ICU delirium was stopped early due to increased mortality in the rivastigmine group.[25] The median duration of delirium, severity of delirium, length of ICU stay, and cumulative doses of *as needed* haloperidol, lorazepam and propofol were all higher in the rivastigmine group. The dosing schedule for rivastigmine was different from the regimen used in Alzheimer's disease, with increases allowed every 2-3 days based on the assumption that correction of the functional cholinergic deficit of delirium would be more rapid than that of chronic dementia.[25] The ACCM advises against using rivastigmine for delirium in adult ICU patients.[2]

PREVENTION STUDIES

General Medical and Surgical Patients

At least three studies have examined prophylactic anti-

psychotic use in patients undergoing orthopedic or gastrointestinal surgery. In a double-blind study, Kalisvaart et al randomized 430 hip surgery patients to receive oral haloperidol or placebo from admission until the third post-operative day.[26] The *incidence* of delirium was similar between groups; however, delirium episodes were shorter and less severe in the haloperidol group. Kaneko et al randomized 78 gastrointestinal surgery patients to receive haloperidol or normal saline IV on post-operative days one through five.[7] The incidence, severity and duration of delirium were significantly lower in the haloperidol group. In a double-blind study, Larsen et al randomized 400 patients undergoing hip or knee replacement surgery to receive one dose of olanzapine or placebo immediately pre- and post-operatively.[13] Delirium incidence was significantly lower in the olanzapine group (14.3% vs. 40.2%, $p < 0.0001$) and more patients in the olanzapine group were discharged to home. Notably, when delirium did occur in the olanzapine group, it lasted longer and was more severe. The latter findings were attributed to the unexpected development of alcohol withdrawal in five of the 28 patients in the treatment group versus none in the control group.

ICU Patients

Two studies have examined prophylactic antipsychotic use in postoperative ICU patients. Prakanrattana et al randomized 126 cardiac surgery patients to receive a single dose of risperidone or placebo postoperatively.[11] Delirium incidence was significantly lower in the risperidone group. Wang et al randomized 457 cardiac surgery patients to receive a continuous infusion of either haloperidol or normal saline postoperatively.[27] Haloperidol treatment was associated with a lower 7-day incidence of delirium, longer time to delirium onset, and a greater number of delirium free-days. A recent meta-analysis of studies examining delirium prevention in general and ICU surgical patients calculated a relative risk of 0.5 for developing delirium in patients receiving prophylactic antipsychotic medication compared with placebo.[7]

Three RCTs have examined the incidence of delirium among ICU patients sedated with dexmedetomidine versus benzodiazepines or opioids. The MENDS trial randomized 106 mechanically-ventilated ICU patients to sedation with dexmedetomidine or lorazepam.[16] The number of days alive without coma or delirium was significantly higher in the dexmedetomidine group. Maldonado et al randomized 118 mechanically-ventilated, cardiac surgery patients to dexmedetomidine, propofol or midazolam sedation protocols.[17] Delirium incidence was significantly lower in the dexmedetomidine group but there were no significant differences in length of ICU or hospital stay. In the DEXCOM study, 306 cardiac surgery patients were randomized to either dexmedetomidine or morphine for sedation and analgesia on admission to the ICU.[18] Delirium incidence was comparable, but dexmedetomidine-treated patients spent three fewer days in delirium, were extubated earlier, experienced less hypotension and required less norepinephrine. Dexmedetomidine use was associated with significantly higher incidence of bradycardia. Dexmedetomidine is an expensive drug, but a recent cost analysis comparing it to midalozam for sedation in mechanically-ventilated ICU patients reported a median savings of $9,679 per ICU stay in dexmedetomidine treated patients.[19]

Two placebo controlled studies reported no benefit of cholinesterase inhibitors for delirium prevention in surgical ICU patients.[6] In contrast, ketamine administered during anesthesia induction was associated with a lower incidence of postoperative delirium compared to placebo in cardiac surgery patients (3% versus 31%).[28]

CONCLUSION

Studies and expert guidelines support the use of antipsychotics for the *treatment* of delirium-related psychosis and agitation. First- and second-generation agents have demonstrated comparable efficacy and safety. Non-pharmacologic interventions significantly reduce delirium incidence, duration and severity. There is growing evidence that antipsychotics and dexmedetomidine are effective in *preventing* delirium in surgical and mechanically-ventilated patients, respectively.

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The 'Problem Patient': Modest Advice for Frustrated Clinicians

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ABSTRACT

"Problem patients" are rare, but they take up a disproportionate amount of clinician time and energy. They often are defined in terms of the effect they have on clinicians rather than any specific behavior – such effects can include frustration, self-doubt and unprofessional behavior. The key to avoiding those pitfalls is to take a deeper look and understand what is behind patients' problematic behaviors. Given the vagueness of the term there are many potential etiologies, most of which are addressable, at least in part. This article presents a brief guide to identifying and managing the various conditions that can cause a disruption of the usually rewarding doctor-patient relationship, and also encourages us to consider the role we might play in this disruption.

KEYWORDS: Problem patient, difficult patient, hateful patient, physician-patient relations, professionalism, conflict (psychology)

INTRODUCTION

'A Typical Problem Patient (Part 1)'

As you pack your children into the car, the physician calls with the psychiatric consult. "The patient is refusing his medication," she says.

"What medication?" you ask.

"Acetaminophen."

"Really, you're calling me because he won't take 'Tylenol'? On a holiday, seriously?"

"Well, his fever is rising and I have to give him something; if I don't control his fever this could get dangerous."

"Well, why is he refusing?"

"I don't know – maybe he's suicidal. Maybe he's just being difficult."

"Well, which do you think it is?"

Irate, she says, "like you said, it's a holiday and I'm the only doctor for this whole service. It's really busy and I don't have time for this. I don't know why he's being so difficult – that's your job to figure out," and abruptly hangs up.

You prepare to tell your children that the parade is off.

THE PROBLEM PATIENT

A PubMed search of the term "problem patient" yields more than 100 articles. Although the term dates back to the 1950s, the definitive treatment of the subject was a now-classic 1978 article by James E. Groves,[1] in which he used a particularly dramatic synonym: the "hateful" patient.

What is a Problem Patient?

Finding a useful definition is elusive. Descriptions in the literature often say less about patients and more about how we react to them.[2] These patients leave us feeling frustrated, angry and helpless. We then feel ashamed at our unprofessional attitude. We may even worry about our ability to provide appropriate care in light of these feelings.

How Should we Approach Such Patients?

First, we must understand them. We need an algorithm, lest we use "problem patient" as if it were an explanation in itself. This article will attempt to organize the different possible etiologies that might account for a patient's seeming attempt to disrupt the normal treatment alliance.

We begin with the most basic of decision points:

Is the Patient's Behavior Deliberate?

Much of our frustration stems from our conviction that a patient's problematic behaviors are "on purpose." Often, this is not the case.* Many disorders can affect a patient's behavior and the ability to cooperate with care. How does one decide? A focused medical interview can inform our hypotheses regarding what might underlie a patient's problematic behavior. One must be careful – provocative metaquestions ("why are you being so difficult?") are rarely helpful, but an empathic inquiry into a patient's behavior can help one assess the level of awareness and control over this behavior.

NON-DELIBERATE BEHAVIORS

Delirium†

Delirious patients may actively resist treatment, sometimes

*It is understood that a discussion of "deliberate behavior" introduces dilemmas regarding concepts of consciousness and free will. These will be deferred to philosophers and this author will not attempt to rise above a lay understanding of these concepts.

† This and the next few diagnoses are discussed in more detail elsewhere in this issue; here the discussion is restricted to a consideration of their role in causing problematic behaviors.

violently; such "agitated patients" are relatively easy to identify. Less dramatic, but more common, are the hypoactive delirious patients who do not resist treatment but cannot consistently participate.[3] They may not take their medications or may not cooperate with physical rehabilitation. In such cases, the critical issue is to recognize the delirium and treat the underlying cause. When the cause is unknown or not easily treated, medications (usually antipsychotics) may help address problematic behaviors, but given their side effects and questionable efficacy, such medications are usually reserved for the most dangerous behaviors. Otherwise, the main treatments are behavioral, emphasizing frequent reassurance and reorientation. Questions of competency may arise, but given that delirium is usually a transient condition, decisions around treatments and disposition should be deferred if possible until the patient is more coherent.

Dementia

The uncooperative demented patient has a more permanent condition that is likely to deteriorate. In the unfamiliarity of the hospital setting, they may become more confused, if not frankly delirious, and the focus should be on returning the patient to their usual baseline. Family members may help determine what that baseline is. Once there, the "problem" in their problematic behavior usually lies in their inability to understand their situation. The priority should be to identify a substitute decision-maker, such as a guardian who can act on the patient's behalf.

Major psychiatric disorders

In addition to cognitive disorders, major psychiatric disorders can impair one's ability to cooperate with treatment. Psychotic patients may not trust their clinicians, depressed patients' negatively distorted world view may cloud their judgment and depressed or anxious patients may lack concentration or seek to avoid stressful decisions altogether. In each case, the focus of treatment should be the psychiatric disorder itself, with the problematic behaviors conceptualized as secondary to the psychiatric illness.

Somatic Symptom Disorders

Although DSM-5[4] has revised the classification of the "Somatoform Disorders,"[5] the central concepts remain the same: there are patients who appear to experience pathological symptoms for which there is no clear medication explanation. In addition, some patients are so worried about having an illness that they cannot function properly. Both types of patients can drain the medical system as well as the patience of their clinicians.

The classic approach to the somatizing patient is to schedule frequent and regular medical visits. This seems simple, but it is contrary to the "problem-driven" focus of modern medicine. To schedule visits regardless of the current status of the patient seems counterintuitive; however, this preventive approach is grounded in behavior theory with its attempt to decrease the association between symptoms and medical attention (for a fuller discussion of the approach to somatic symptom disorders, see Oyama et al[6]).

DELIBERATE BEHAVIORS

Factitious disorder and malingering

At times, we suspect patients are lying to us. Usually they are not, but rarely patients do deliberately fabricate their medical history or symptoms. Lying is not a medical or psychiatric disorder, it is a common human behavior – the issue here is the motivation for the behavior.

A patient with factitious (or Munchausen) disorder fabricates symptoms: the reasons for this are not clear but presumably derive from a desire to be treated as a patient. Most of us are familiar with the care and attention that come with being a patient; few of us, however, are willing to lie or fake symptoms to obtain this. Our understanding of those who do is poor; however, it is assumed that most have underlying severe psychiatric disorders.

Malingering is simpler, in that patients lie for some rational (that is, easily understandable and identifiable secondary) goal: money, relief from responsibility, shelter or protection for example. It is *not* a disorder, it *is* "bad" – but usually understandable – behavior. It need not occur as part of another psychiatric disorder, and although we associate malingering with sociopathy, this is not always the case: we can all empathize with a homeless patient who presents to an emergency department with vague symptoms in a desperate attempt to get out from the cold.

At times, the "practical" goals associated with malingering can overlap with a desire to assume the patient role, and differentiating malingering from factitious disorder can be challenging, particularly as it seems to require us to look into the hearts and minds of our patients to discern their motivations. It may be helpful to remember that patients with factitious disorder are often very psychologically ill people who may have a number of comorbid psychiatric disorders (particularly personality disorders) requiring careful assessment and an offer of treatment, whereas as noted above, malingering can be independent of any other psychiatric disorder.

Many clinicians find untruthful patients to be particularly trying; however there is no benefit from taking an unprofessional stance. It is usually best to avoid direct confrontation, which is likely to be met with anger, denial and an abrupt discharge against medical advice. Patients should be approached forthrightly and empathically in an attempt to clarify the diagnosis and engage the patient in a treatment that includes education about the disorder and its potential consequences (C Harrington, personal communication). It may be useful to consider what the patient seeks to gain from their behavior and it may be helpful to address this goal, particularly if the behavior is not part of a larger personality issue. A patient seeking shelter, for example, may

not be aware of the options available and providing practical assistance is not only kind, but likely to decrease their reliance on the medical system for survival. Most important, is to do no harm, by, for example, performing unnecessary diagnostic procedures or starting unnecessary medications.

Personality Disorders

Personality disorders include, by definition, difficulties with normal relationships. It should be no surprise, then, that these patients interact poorly with the medical system. Instead of DSM-5's rigid categories, it may be more helpful to use Grove's original approach[1] by recognizing certain broad personality types that have particular difficulties with the medical system:

The Dependent Clinger: These patients require an unreasonable degree of explanation and attention that challenges a clinician's professionalism, as well as one's time-management skills. The usual inclination to appease a patient fails in light of their bottomless pit of need, resulting in mutual frustration and anger.

The Entitled Demander: These patients seek attention through intimidation and devaluation. They may demand tests, refuse payment, or threaten legal proceedings. Clinician reactions can range from helplessness to defensiveness to outright malevolence.

The Manipulative Help-Rejecter: Although professing to want medical help, these patients are more interested in the relationship with their clinicians. Improvement risks losing that relationship, thus they remain ill. They may justify their noncompliance by devaluing their clinicians, leaving them to feel guilty or inadequate.

The Self-Destructive Denier: Unlike Help-Rejecters, who desire a clinical relationship, the self-destructive patient seems motivated only by a desire for self-harm. These patients can challenge the essence of our professional ethic – our desire to help the sick – and our resulting frustration can lead to anger and a wish to abandon these patients.

Such categories derive more from clinical wisdom than empirical investigations, and only roughly correlate with the (recently abandoned) DSM symptom clusters. For example, some Entitled Demanders might belong in the prior DSM's "dramatic cluster" whereas the more dependent ones would belong in the "anxious" cluster; however, obtaining an official diagnosis is probably less important than recognizing the patterns of behavior, in order to guide therapeutic responses to these patients.[7]

There is no simple method to successfully treat each of these patients, but the key is to first recognize and then understand them.[8] The unaware clinician risks either adopting the patient's point of view or feeling personally attacked. Once recognized, the clinician can step back and realize that the behaviors are part of a larger interpersonal problem affecting all areas of a patient's life.[9] It may also help to realize that some of the unpleasant feelings experienced by the clinician provide insights into the degree of inadequacy and self-hatred that the patient experiences every day. Understanding this can, hopefully, encourage empathy (or, at least, sympathy) and professional distance. Once achieved, the clinician can decide on an appropriate treatment plan, as well as appropriate boundaries and limits to the professional interaction.

CODA: WHEN THE PATIENT ISN'T THE PROBLEM

'A Typical Problem Patient (Part 2)'

Walking into the patient's room, you see him comfortably lying in his hospital bed, watching the very basketball game you were listening to as you drove to the hospital. A few questions about the game convince you that he is cognitively intact and his animated and intelligent discussion of the game start to make depression or some other psychiatric disorder seem unlikely. Getting down to business, you tell him, "the reason I'm here is that your doctors are concerned that you won't take your medications."

"That again?" he says with exasperation.

"Well," you explain, "apparently they think you really need the acetaminophen – why are you refusing it?"

"Because I have cirrhosis," he answers. "I've had it for years, and the doctor who diagnosed it told me I should never use Tylenol again."

You admit that the explanation makes perfect sense.

Later, you find the consultee, who admits that she forgot about the patient's liver disease, but is unapologetic, saying that she had a long night on call, and that the patient's inappropriate flirtatiousness combined with a questioning of her expertise during her initial evaluation caused her to cut the interview short.

Sometimes, the "problem" lies with us. One large general medical survey found that physicians who reported high frustration with patients were less experienced, worked longer hours and had more symptoms of depression, stress and anxiety than other doctors.[10] Fatigue, stress and burnout can affect our ability to maintain a professional demeanor.

Even at our best, there will always be patients who "push our buttons."

Before branding a patient as a problem, we should examine ourselves, our reaction to the patient and consider why we are having that reaction. It is helpful to avoid assigning fault, and instead seeing a problematic relationship as a mutual "failure to communicate." Reestablishing rapport should be the overriding issue. Then, the clinician must work to create a trusting, empathic and professional relationship. Even when a patient does fit into one of the categories of "problem patient" listed here, this approach will be more fruitful than explaining (or dismissing) a patient with a label.

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Serotonin Syndrome: A Concise Review of a Toxic State

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ABSTRACT

The serotonin syndrome is a toxic state caused by increased intrasynaptic serotonin and characterized by a triad of altered mental status, autonomic instability and neuromuscular abnormalities. It can result from exposure to a single serotonergic agent but is more likely to be due to polypharmacy, often with drugs from multiple classes. It develops over a short period of time and resolves just as quickly once identified and treated. Diagnostic criteria have been developed to assist in clinical practice. Treatment is largely supportive and prognosis is generally very favorable. Pharmacologic vigilance and prevention are key.

KEYWORDS: Serotonin syndrome, polypharmacy, myoclonus

INTRODUCTION

Frequently considered diagnostically but not always recognized or well understood, the serotonin syndrome (SS) is best conceptualized as a potentially life-threatening neurotoxic state rather than a distinct idiosyncratic reaction. It results from excess intrasynaptic serotonin, with symptoms developing over hours, and is characterized by the triad of mental status alteration, neuromuscular hyperactivity and autonomic instability.[1,2]

Initially described in 1960[3] and brought into mainstream awareness with the case of Libby Zion,[4] its true incidence is likely underestimated given the wide spread use of selective serotonin reuptake inhibitors (SSRIs) and other serotonergic drugs, and because mild cases often go undetected.[2,5] Serotonin syndrome occurs in approximately 14%-16% of patients who overdose with SSRIs.[6]

Serotonin syndrome has been reported to occur with numerous drugs and in various combinations, and is overwhelmingly the result of polypharmacy, including illicit and over-the- counter drugs (OTCs). Occurrence of SS with a single agent is unusual, though it does occur, sometimes after a single dose.[7] Case reports document numerous drugs from different classes as precipitants for this toxic state.[8-12]

In this article we review the pathophysiology, clinical presentation, differential diagnosis, precipitating drug classes, and general management of the SS. The aim of this paper is to provide a brief review of the SS in order to promote greater awareness, increased understanding, and more effective prevention of this toxidrome.

PATHOPHYSIOLOGY

Serotonin (5-hydroxytryptamine or 5-HT) is a product of hydroxylation and decarboxylation of L-tryptophan.[8] The majority of serotonin is found in the periphery where it is involved in regulation of GI motility and vasomotor function. Approximately 2% of serotonin is found in the CNS and synthesized primarily in the raphe nucleus of the brainstem.[13] Serotonin is involved in modulating multiple CNS functions including core body temperature, emesis, eating behavior, analgesia, wakefulness, sexual behavior, mood, affect, perception, and personality.[2,8,14,16]

The SS toxidrome is thought to result from hyperstimulation of postsynaptic serotonergic receptors. Clinical findings do not correlate with serum serotonin levels; it is the concentration at the nerve terminal that is most important. While 5-HT2A receptor agonism has been implicated,[2,8,15,16] activation of the 5-HT1A receptor is thought to be primarily responsible for the clinical syndrome.[2, 8, 13-14, 16-18] Increased serotonergic activity is driven by various mechanisms including increased serotonin synthesis and release, decreased catabolism and reuptake, and increased receptor agonism and sensitivity.[8,14,19]

Genetic variability in the activity of the monoamine oxidase (MAO) enzyme responsible for serotonin metabolism is a predisposing factor for the development of SS. Acquired defects in MAO activity and serotonin metabolism related to cardiovascular disease, liver disease, and pulmonary disease associated with chronic tobacco use are identified risk factors for SS development.[18]

Drugs and drug classes that can contribute to the development of this toxic state include, but are not limited to: opioids (and related agents including tramadol), antimicrobials (including antiretrovirals), SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), atypical antidepressants such as trazodone and mirtazapine, lithium, triptans, anxiolytics, antihistamines, antitussives, anti-emetics, antiepileptic drugs (AEDs), muscle relaxants, anti-obesity drugs, methylene blue, herbal preparations, OTCs, and drugs of abuse.[8,19]

CLINICAL PRESENTATION AND DIAGNOSIS

SS is a clinical syndrome that requires a careful history, complete medication reconciliation, and comprehensive physical and mental status examinations to diagnose. It presents with a triad of mental status changes (anxiety, agitation, confusion, restlessness, disorientation, coma), neuromuscular abnormalities (rigidity, tremor, nystagmus, myoclonus, hyper-reflexia, ataxia, increased tone, particularly in the lower extremities), and autonomic instability (hypertension, hypotension, tachycardia, tachypnea, mydriasis, diaphoresis, hyperthermia).[5, 14-15, 17, 20]

The majority of cases present within 24 hours, and most within six hours of starting, changing, adding, and even withdrawing a drug.[21] Clinical presentation varies across a spectrum of severity. Mild cases can present with only anxiety and tremor and often go undetected. When severe, SS can present with hyperthermia, rhabdomyolysis, acute renal failure, metabolic acidosis, disseminated intravascular coagulation, respiratory failure, seizure and coma. Fatalities associated with SS are often the result of poorly treated hyperthermia.[11,12,19] Associated laboratory findings are non-specific, and can include elevated aminotransferases, creatinine, serum potassium, and creatinine phosphokinase (CPK), as well as leukocytosis, and myoglobinuria.[12,19]

The differential diagnosis of SS is broad and includes malignant hyperthermia, anticholinergic toxicity, opioid withdrawal, CNS infection, delirium tremens, non-convulsive seizures, sympathomimetic toxicity, stiff man syndrome, and heat stroke, but diagnostic consideration of neuroleptic malignant syndrome (NMS) in patients treated simultaneously with dopamine blocking agents is most common and challenging.[8,14] A number of findings aid in the differentiation between SS and NMS including abrupt onset, rapid resolution, mydriasis, myoclonus, hyper-reflexia, and clonus (especially in the lower extremities) in SS[2,14] (**Table 1**).

Several diagnostic criteria have been developed for the accurate identification of SS.[17, 22] The Hunter criteria[20] provide decision rules that are simple to apply and have been shown to have good sensitivity (75%) and specificity (86%) (**Table 2**).

Table 1. Differentiating SS from NMS.

	SS	NMS
Onset	Abrupt > gradual	Gradual > abrupt
Course	Rapid resolution	Prolonged
Neuromuscular findings	Myoclonus + tremor	Diffuse rigidity
Reflexes	Increased	Decreased
Pupils	Mydriasis	Normal

Table 2. The Hunter criteria for serotonin syndrome.

Presence of a serotonergic agent *plus one* of the following:
Spontaneous clonus.
Inducible clonus + agitation or diaphoresis.
Ocular clonus + agitation or diaphoresis.
Tremor + hyperreflexia.
Hypertonia + temperature >38°C + ocular or inducible clonus.

TREATMENT

Successful treatment is based on prompt recognition, after which the offending drug(s) are removed and supportive treatment instituted. Serotonin syndrome has a generally favorable prognosis and often resolves without specific intervention, other than supportive measures, including intravenous hydration and provision of a safe environment for the management of delirium.[24, 25] Most cases resolve within 24 hours. In approximately 30%-40% of cases, however, symptoms persist beyond 24 hours and may require more intensive care.[16]

Beyond supportive measures in mild cases, level of intervention is based on severity of presentation. Agitation is treated with benzodiazepines and external cooling is used to prevent complications of hyperthermia.[14] Moderate symptoms may be treated pharmacologically with cyproheptadine, a 5-HT2A antagonist and nonselective H1 antagonist.[23,25] Chlorpromazine, a 5-HT2A antagonist and dopamine antagonist, is a second-line agent, but caution is advised due to the risk of hypotension and the drug's ability to decrease the seizure threshold. In cases where NMS is a diagnostic consideration, chlorpromazine and other dopamine blocking agents should be avoided so as to minimize diagnostic confounding.

Significant neuromuscular hyperactivity and autonomic instability suggest a severe course of illness and require aggressive treatment that may include sedation, intubation, and paralysis. Succinylcholine should not be used in cases of rhabdomyolysis to avoid exacerbation of hyperkalemia. Restraints should be avoided as they are associated with isometric muscle contraction that can drive lactic acidosis and worsen hyperthermia. Bromocriptine and dantrolene sodium, used in cases of severe NMS, have no proven role in the treatment of SS. Antipyretics are not indicated as hyperthermia in SS is thought to be due to excessive muscle contraction rather than to a change in hypothalamic set point.

Reinstitution of serotonergic drugs and other potentially offending agents needs to be carefully considered according to specific clinical indications and risk of recurrent toxicity. Serotonin syndrome is much easier to prevent than to treat.

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Practical Management of Alzheimer's Dementia

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. There currently is no effective treatment that delays the onset or slows the progression of AD. Significant advances in neuroscience, genetics and molecular biology over the past 25 years have changed the way we think about AD. This article reviews the literature on diagnosis and treatment of AD so that primary care physicians can manage this complex disease.

KEYWORDS: Alzheimer's disease, dementia, dementia medications

INTRODUCTION

Every 68 seconds, a person in the United States is diagnosed with Alzheimer's dementia (AD). By 2050, this rate is expected to double. An estimated 5.2 million Americans currently have Alzheimer's dementia, and it is predicted that by 2050 that number will approach 13.8 million.[1] AD has emerged as a serious public health concern, placing an immense burden on patients, families, the community, and health care resources. AD accounts for approximately 60% of all cases of dementia in the developed world. The focus of this review will be on practical management of primary care patients with probable AD.

A common misperception is that AD is a normal or expected occurrence of aging, and that it is part of the typical trajectory of age-related cognitive decline. Healthy aging has been found to be associated with generally stable performance on measures of cognitive functioning, such as the Mini-Mental Status Examination (MMSE). However, as individuals live to advanced ages (over the age of 80), it is more challenging to differentiate between the subtle changes of aging and those caused by early dementia. Unfortunately, family members and caregivers may fail to recognize or be in denial about the significance of their loved one's cognitive decline, leading to delayed diagnosis and late treatment of dementia when behavioral problems become problematic or unmanageable. Pathologic changes that underlie AD begin to accumulate decades before cognitive and behavioral changes emerge.[2] Markers of brain health versus cognitive decline may be identifiable earlier in life. In the seminal Nun Study published in JAMA,[3] approximately 80% of nuns whose early-life writing samples were measured as lacking in complexity went on to develop Alzheimer's disease in old age as opposed to 10% of those whose writing was rated as more complex.

Nearly a hundred years ago, post-mortem analysis of human AD brains provided the first clues to the pathophysiology of AD and potential interventions. Senile plaques composed of extracellular deposits of amyloid-β (Aβ) and neurofibrillary tangles formed by intracellular aggregation of phosphorylated tau protein were found in regions of cortex that serve memory and other cognition functions. Based upon demonstrated deficiencies in choline acetyltransferase, the enzyme responsible for the synthesis of acetylcholine, the "cholinergic hypothesis" of AD was proposed.[4] The more recent "amyloid cascade" hypothesis of AD proposes that Aβ, specifically the least soluble forms Aβ 40 and 42, have a central role in AD. Aβ 40 and Aβ 42 are cleaved from amyloid precursor protein (APP) by beta and gamma secretase enzymes known as presenilin 1 and 2. Innovative studies over the last decade have evaluated enzyme inhibitors and immunotherapies that interfere with Aβ production, inhibit Aβ aggregation, and enhance Aβ clearance. Evidence for the reduction of amyloid and related AD pathology by these agents in transgenic mouse models has been very encouraging. Unfortunately, phase III human trials have been disappointing, including a recent trial of bapineuzemab, a human anti-Aβ monoclonal antibody, that failed to show benefit.[5] These and other basic science mechanisms operative in AD and novel treatment approaches are reviewed elsewhere.[6] Therapies targeting amyloid-based pathology have dominated recent drug development. Trials of tau-based therapies are newly underway.

Mutations in three genes – APP, presenilin 1 and presenilin 2 – all predispose to early onset (autosomal dominant) AD. In Trisomy 21, where there is duplication of the APP gene on chromosome 21, symptoms of AD may begin in the third or fourth decade of life. The E4 allele of the apolipoprotein E (APOE) gene has been identified as a major risk factor for late-onset AD.[7] No specific environmental toxin has been consistently associated with AD.

DIAGNOSIS

AD typically progresses along a continuum from normal aging to amnestic, mild cognitive impairment (a-MCI) and

finally frank AD. Patients with a-MCI present with memory deficits that are greater than would be expected based on age and education; however, functional abilities remain intact and behavioral problems are rare. Amnestic-MCI progresses to AD at a rate of 5-15% per year. There are no FDA-approved treatments for a-MCI. In a 3-year placebo controlled trial, Peterson et al evaluated vitamin E 2000IU and donepezil 10mg for the treatment of MCI. Donepezil reduced the rate of conversion to AD at 12 months, but neither agent separated from placebo at three years.[8] Nonetheless, this stage presents an opportunity for closer follow-up, modification of pre-morbid risk factors such as smoking, diabetes, and depression, and education and empowerment of the patient and family. Early diagnosis provides the patient and family an opportunity to anticipate problems and plan for the future (e.g., advanced health care wishes, wills) while the patient is still capable of making medical decisions.

A thorough history should be taken, preferably with a knowledgeable spouse or other family member present, in order to determine the time of onset and the course of cognitive decline. Recommended diagnostic tools include the Mini-Mental Status Examination (MMSE), the Clinical Dementia Rating Scale (CDR), and formal neuropsychological testing. Although neuropsychological testing remains the gold-standard for diagnosis, it is expensive and not available to all patients. No laboratory or imaging tests are sufficient to diagnose AD, although they may rule out reversible causes of dementia such as Vitamin B-12 deficiency, thyroid disease, electrolyte abnormalities, and certain structural lesions.

CT and MR imaging of AD typically demonstrate cerebral volume loss, especially in the temporal lobe structures such as the hippocampus. Brain single-photon emission computed tomography (SPECT) and fluorodeoxyglucose positron emission tomography (FDG-PET) studies in AD typically demonstrate, respectively, reduced cerebral blood flow and hypometabolism in posterior temporo-parietal regions. New biomarkers, such as cerebrospinal fluid measures of amyloid-β42 and phosphorylated tau have demonstrated impressive sensitivity and specificity in diagnosis of AD, but neither is utilized in routine practice or universally supported by published guidelines. In 2012, a PET scan that selectively binds amyloid-β plaques was approved by the FDA for AD testing. Unfortunately, this test is still not covered by the Centers for Medicare or Medicaid Services or any private insurers.[9] This test should be reserved for patients with early-onset cognitive dysfunction (usually defined as 65 years or less in age), atypical clinical presentations or course of illness, or other unexplained cognitive decline.[10]

PHARMACOLOGIC TREATMENT OF COGNITIVE SYMPTOMS

There are no available therapies that can stop or reverse the course of AD. The pharmacologic agents approved for the treatment of AD remain limited and include the three cholinesterase inhibitors (ChEI) donepezil (Aricept™), rivastigmine (Exelon™), and galantamine (Razadyne™) and a single N-methyl-d-aspartate receptor antagonist, memantine (Namenda™). The ChEI are approved for all three stages of AD, from mild to severe, and serve primarily to reduce the rate of cognitive decline. Memantine is approved for moderate to severe AD. Studies suggest no benefit from memantine in early disease. The American Psychiatric Association (APA) recommends that all patients with mild to moderate AD be offered treatment with a ChEI. Consistent with recent FDA approval of ChEIs for severe AD, the APA suggests

Summary of all the available FDA-approved medications for Alzheimer's dementia

Generic Name	Trade Name	Indication	Available Formulations	Start dose	Target dose	Renal dosing	Hepatic dosing
Donepezil	*Aricept*™	Mild-mod AD: 5,10mg Mod-severe AD: 10mg, 23mg	5, 10mg tabs 5, 10mg ODT 23mg tabs	5mg QD	10mg QD	No change	No change
Galantamine	*Razadyne*™ *Razadyne ER*™	Mild to moderate AD Mild to moderate AD	4,8, 12mg tabs 4mg/ml sol'n 8,16,24 mg caps	4mg BID 8mg QD	12mg BID 24mg QD	16mg max	16mg max
Rivastigmine	*Exelon*™ *Exelon Patch*™	Mild to moderate AD Mild to severe AD	1.5,3,4.5, 6mg caps 2mg/ml sol'n 4.6,9.5,13.3mg patch	1.5mg BID	6mg BID	No change	No change
Memantine	*Namenda*™ *Namenda XR*™	Moderate to severe AD Moderate to severe AD	5, 10mg tabs 7,14,21,28mg tabs	5mg QD 7mg QD	10mgBID 28mg QD	5mg BID max	No change

Summary of SGAs used in dementia-related psychosis and agitation

Generic Name	Trade Name	Available Formulations	Start dose	Typical dose	Common side effects
Aripiprazole	Abilify™	2,5,10,15,20,30mg tablets 10,15mg ODT 1mg/ml oral sol'n 9.75mg single dose injection	2mg	5-10mg	Somnolence, EPS, fatigue, nausea, akathisia Least likely to cause QT prolongation
Olanzepine	Zyprexa™	2.5,5,10,15,20,30mg tabs 10mg,15mg ODT 10mg single dose injection	2.5mg	5-10mg	Postural hypotension, constipation, weight gain, dizziness Doses >10mg/day may cause anticholinergic side effects
Quetiapine	Seroquel™	25,50,100,200,300,400mg tabs	12.5mg	25-50mg	Somnolence, dizziness, nausea, fatigue Least likely to cause parkinsonism
Risperidone	Risperdal™	0.25,0.5,1,2,3,4mg tabs 0.5,1,2,3,4mg ODT 1mgl/ml oral sol'n	0.5mg	1-2mg	Parkinsonism, akathisia, dystonia, tremor, sedation
Ziprasidone	Geodon™	20,40,60,80mg tabs 20mg/ml single dose injection	20mg	40-60mg	Somnolence, EPS, dizziness May cause significant QT prolongation

consideration of cholinergic therapies in late disease as well.[11] Evidence suggests that ChEI treatment for at least six months delays the need for nursing home admission.[12] There are reports of marked improvement in cognitive and neuropsychiatric status with initiation of cholinesterase inhibitors in cases of dementia with Lewy bodies (DLB), perhaps consistent with pathologic observations of more significant loss of cholinergic neurons in DLB. Rivastigmine is FDA-approved for PD dementia, though its clinical benefits are modest.

There are no specific recommendations regarding the discontinuation of ChEIs or memantine. Some reports suggest subacute cognitive deterioration when these agents are abruptly stopped. Typical practice in the US includes early treatment with a ChEI and addition of memantine when disease progresses to the moderate-to-severe stage. Howard et al compared continued treatment with donepezil alone to addition of memantine to donepezil and memantine alone (after donepezil discontinuation) in moderate-to-severe AD. Continued treatment with donepezil alone and memantine alone were associated with similar cognitive benefit compared to placebo. In contrast to earlier studies, the combination of donepezil and memantine provided no additional benefit compared to continued donepezil alone.[13]

The most common adverse effects of ChEIs include nausea, vomiting, diarrhea, anorexia, insomnia, muscle cramps, and fatigue. Less common, but notable side effects of ChEIs include nightmares, weight loss, gastrointestinal bleeding, symptomatic bradycardia, and syncope. Rivastigmine is available as a once-daily transdermal formulation, *Exelon patch*™, that may improve gastrointestinal tolerability. Memantine is typically dosed at 10 mg twice daily. Namenda™ is now available in a 20 mg XR formulation that is intended for once daily dosing. Adverse effects of memantine include fatigue, dizziness, constipation, headache and occasionally worsening of AD-related behavioral problems.

NEUROPSYCHIATRIC-BEHAVIORAL SYMPTOMS AND THEIR PHARMACOLOGIC TREATMENT

Behavioral symptoms in dementia are common and include anxiety, apathy, depression, irritability, agitation, aggression, delusions, and hallucinations. The occurrence of these symptoms varies depending on the cause and stage of dementia. Apathy, irritability, and depression are common in early dementia while agitation, delusions, and hallucinations tend to occur in the later stages of the disease.[14] Aggressive behaviors can be verbal and physical. It is often difficult to distinguish between psychotic and non-psychotic forms of aggression.

Depression is often a harbinger of dementia in patients with no prior psychiatric history of a mood disorder. Indeed, late-onset depression may represent a presenting behavioral syndrome of an overarching neurodegenerative disorder

such as AD or vascular dementia. The evidence base for pharmacologic treatment of depression in dementia patients is limited. SSRIs are considered first line agents for treating depression in dementia patients.[15] Sertraline and citalopram have minimal pharmacokinetic interactions and are particularly indicated in elderly patients who are often on multiple medications. SSRIs have a broad range of additional effects including attenuation of anxiety, irritability, hostility, and obsessions and compulsions. Compared to placebo, citalopram (Celexa™) at 30mg daily significantly reduced agitation and caregiver distress in patients with probable AD.[16] Mild decline in cognitive performance and mild prolongation of the QTc interval (mean 18 msec) were noted in the citalopram-treated group.

Tricyclic antidepressants (TCAs) are associated with numerous adverse effects including cardiac arrhythmias, urinary retention, constipation, delirium, and overdose risk and should be used with caution in dementia patients. The anti-cholinergic effects of TCAs may be additive to the cholinergic loss of AD and exacerbate cognitive dysfunction. Mirtazapine (Remeron™) may be particularly effective in addressing complaints of poor appetite and insomnia that are common in depressed AD patients. There is some evidence that ChEIs can improve mood and other non-cognitive behavioral symptoms in AD. For this reason, a trial of a ChEI targeting both cognitive and neuropsychiatric symptoms in behaviorally dysregulated AD patients makes sense before the addition of a primary psychotropic agent. A trial of stimulants, such as methylphenidate, may be warranted in those patients with prominent apathy or those who partially respond to SSRIs.

Neuropsychiatric symptoms of agitation, aggression, and psychosis are associated with global decline in patient function and have a very negative effect upon caregiver and family quality of life.[17] These symptoms typically evolve over months; but when they emerge abruptly, it is important to evaluate for a diagnosis of delirium. Delirium is particularly common in demented patients. Medications with anticholinergic properties, benzodiazepines, and narcotics are often implicated as causes of delirium atop a baseline dementia. Uncontrolled pain, constipation, malnutrition, dehydration, and infection, particularly urinary tract infections, may also precipitate delirium. It is imperative that these conditions are addressed before assuming that agitation is due primarily to underlying AD or disease progression.

Although there are currently no FDA-approved agents for the treatment of dementia-related agitation and psychosis, second-generation antipsychotics (SGA) have been utilized to treat these symptoms. A recent study of Medicare beneficiaries in nursing homes found that 27% were prescribed antipsychotics.[18] The use of these medications in dementia management remains controversial, especially in light of the 2005 "black box" warning. Schneider et al found a significant increase in cerebrovascular events, especially with risperidone, when using SGAs for the treatment of agitation and psychosis in demented nursing home patients.[19] Additional analysis of the data documented an increase in all-cause mortality in dementia patients treated with SGAs compared to placebo. Antipsychotic use in dementia has declined since the issuance of this warning, particularly in nursing homes.

There is a limited evidence base regarding the effectiveness of SGAs for the treatment of dementia-related agitation and psychosis. The CATIE-AD trial examined the effectiveness of the three most commonly used SGAs – quetiapine, risperidone, and olanzapine. All of these agents, but particularly olanzapine, were associated with significant weight gain. Sedation and confusion were common side effects of all three medications. Olanzapine and risperidone were associated with Parkinsonism and other extra-pyramidal symptoms (EPS). Quetiapine was relatively free of EPS side effects. The CATIE-AD trial concluded that the adverse effects of these medications may outweigh any benefit they provide for the treatment of behavioral symptoms in dementia patients. Given their "black box" warning, SGAs are likely best reserved for patients with prominent psychosis and/or agitation who have not improved with non-pharmacologic treatments, cholinesterase inhibitors, or SSRIs. If ineffective, these agents should be discontinued rather than adding a second drug. Even when clinically beneficial, noting the evolving course of the underlying dementia, SGAs should be periodically tapered or discontinued to reassess their indication. Typical suggested starting doses of these drugs include risperidone 0.5mg, quetiapine 25mg, or olanzapine 2.5mg, all dosed once daily at bedtime. Given the limited evidence base and the warning regarding the use of these agents in dementia, careful informed consent discussion with patient and family about the risks and benefits of treatment versus the risks of untreated agitation should precede the initiation of any antipsychotic medication.

Behaviors such as wandering, yelling, and stubbornness can be particularly difficult to manage, often precipitate nursing home placement, and frequently persist in the institutional care setting. It is important that medication not be used as a "chemical restraint" to control these relatively benign behaviors. A multidisciplinary approach with input from properly trained nursing staff, social workers, and family can be helpful in designing a non-pharmacologic plan to help manage these behaviors. Novel approaches such as aromatherapy are being increasingly utilized in long-term care with success.[20]

Psychosocial interventions include cognitive and social stimulation such as adult day care participation, behavioral-oriented therapies, and caregiver support. Since activities of daily living (ADLs) such as self-care, personal hygiene, and dressing tend to worsen with progression of AD, patients with advanced AD require a greater level of caretaker commitment. Management of medical decisions and financial affairs, and cessation of driving often emerge as problems for caregivers. It is important to provide adequate caregiver

support, as "caregiver burden" is associated with high rates of AD patient nursing home placement.[21] Caregivers often benefit from referral to Alzheimer's Association support groups. When at-home care is no longer viable, families face the difficult decision of placing their loved one in an assisted-living facility or nursing home. The onset of behavioral problems such as aggression and delusions, rather than frank cognitive decline proper, often hastens this transition to long-term care.

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Emerging Drugs of Abuse: Clinical and Legal Considerations

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ABSTRACT

Over the past several decades, nontraditional drugs of abuse, including bath salts, synthetic cannabinoids, and salvia, have increased in popularity and use. Despite this fact, they remain unfamiliar to many healthcare providers. Commonly marketed as "legal highs," these substances are being used for their desired neuropsychiatric effects, taking advantage of their accessibility, low cost, variable legality, and limited detection on traditional urine drug screens. Similar to traditional drugs of abuse, these substances have varying degrees of toxicity and may lead to potentially adverse effects, ranging from benign to life threatening. This paper offers a review of three of the more widely-used emerging drugs (or classes of drugs): bath salts, synthetic cannabinoids, and salvia. For each we review its history and development, the neurochemical basis for its clinical effects, the nature and route of ingestion, the range of desired effects, potential toxicities, diagnostic and therapeutic approaches, as well as social and legal considerations.

KEYWORDS: Emerging drugs, drug abuse, bath salts, salvia, synthetic cannabinoids

INTRODUCTION

The past decade has been witness to a growing number of drugs of abuse. These include designer drugs, which are synthesized to mimic the structure and/or psychoactive properties of existing substances, and herbal substances, which contain one or more molecules that elicit a range of psychoactive effects. The prevalence of the use of these drugs and a growing understanding of their toxicity has sparked concern among medical and public health professionals alike. Of additional concern is the manner in which many of these drugs are advertised and sold. They are commonly marketed as "legal highs" with packaging that appeals to youth and young adults, and are relatively inexpensive, readily available online, in "head shops," at gas stations and convenience stores, and are not detected by standard drug screens. Keeping legal regulations at pace with the development of these drugs has proved challenging. Although the Synthetic Drug Abuse Prevention Act of 2012 added 15 synthetic cannabinoid receptor agonists and 11 synthetic cathinones to Schedule I of the Controlled Substances Act,[1] new analogues continue to be developed to evade this and other state-specific bans.

This paper offers a review of three of the more widely-used emerging drugs (or classes of drugs): bath salts, synthetic cannabinoids, and salvia. For each substance, we will outline its history and development, the neurochemical basis for its clinical effects, the nature and route of ingestion, the range of desired effects, potential toxicities, diagnostic and therapeutic approaches, as well as social and legal considerations (**See Table 1**).

Bath salts

Background

'Bath salts' is a general term referring to more than 30 available synthetic derivatives of cathinone[2] which was identified in 1975 as the principal psychoactive component of Khat.[3]

Table 1. Summary of desired effects, toxicities and management

	Desired effects	Toxicities	Management
Bath salts	○ Stimulation ○ Elation ○ Friendliness ○ Fluency ○ Sexual arousal ○ Perceptual disturbances	○ Sympathetic overstimulation ○ Aggression ○ Agitation ○ Memory deficits ○ Hallucinations ○ Paranoia	○ Supportive measures ○ Low-stimulation environment ○ Benzodiazepines, ○ IV fluids ○ Brief low-dose antipsychotics for psychosis only
Synthetic cannabinoids	○ Euphoria ○ Relaxation ○ Disinhibition ○ Altered perception ○ Altered consciousness	○ Anxiety ○ Mood dysregulation ○ Memory deficits ○ Hallucinations ○ Paranoia ○ Seizures ○ Nausea/vomiting ○ Diaphoresis ○ Hot flushes ○ Mydriasis ○ Tremor ○ Tachycardia ○ Hypertension	○ Supportive measures ○ Low-stimulation environment ○ Benzodiazepines
Salvia	○ Trance-like state ○ Hallucinations ○ Sensory disturbances ○ Synesthesia ○ Extra-bodily experiences ○ Elevated mood	○ Depersonalization ○ Anxiety ○ Dysphoria ○ Confusion ○ Fear ○ Headaches ○ Drowsiness ○ Tachycardia ○ Hypertension	○ Supportive measures ○ Low-stimulation environments ○ Benzodiazepines

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Bath salts

Cathinones have been investigated for their stimulant, antidepressant and appetite suppressant properties, but such studies have been halted because of concerns for abuse and dependence.[2,3] Mephedrone, MDPV (3,4-methylenedioxypyrovalerone) and methylone are the most common recreationally-used cathinones because of their structural, and clinical, similarities with amphetamine.[4] They are most widely produced in China, Pakistan and India and are typically sold as powder or pellets. Bath salt can be administered by oral, intranasal, inhaled (smoked), intravenous, or rectal routes.[3]

Mechanism of action and neurochemical considerations

Bath salts exert their effects by inhibiting vesicular monoamine transporters for serotonin, dopamine and norepinephrine, thereby increasing presynaptic neurotransmitter levels.[5] They also act as potent monoamine oxidase (MAO) inhibitors, with increased selectivity for MAO-B.[6] When compared to amphetamine and MDMA, bath salts were found to produce a greater increase in serotonin and dopamine levels in the nucleus accumbens.[2]

Desired effects, toxicities and long term effects

Although the pharmacokinetic properties of bath salts vary with the specific analogue used, the average onset of subjective effects occurs within 30 minutes. Effects peak at 45 to 90 minutes after administration and last up to 3 hours. The subjective effects include stimulation, elation, friendliness, talkativeness, sexual arousal and perceptual disturbances.[7]

Adverse neurobehavioral reactions include anxiety, hallucinations, delusions (paranoid and other), agitation, aggression, impaired working memory, and bruxism.[4] Bath salts have also been associated with metabolic derangements including hyponatremia, rhabdomyolysis, disseminated intravascular coagulation, acute kidney injury, and hepatic failure.[4] Additional toxicities range from sympathetic overstimulation (including hypertension, tachycardia, and hyperthermia) to seizures and death.[4,8] Cases of excited delirium, known as "bath salts psychosis," have been reported and are associated with significant mortality.[8,9] Bath salts withdrawal symptoms include depression, impulsivity, anhedonia with cognitive complaints of poor concentration and attention.[15] Long-term bath salt use is complicated by tolerance and a marked tendency to re-dose, thereby increasing the risk for accidental overdose.[2]

Diagnostic and therapeutic considerations

Bath salts are not detected by standard urine toxicology tests. Mass spectroscopy and gas chromatography can be used to detect specific cathinones but these tests are expensive.[7] Result reporting from these methods is often delayed, making them less helpful in guiding differential diagnosis and treatment during the acute phase of illness.[7] At present, there are no validated guidelines for the management of acute bath salts intoxication but current recommendations include supportive measures, low stimulation environments, benzodiazepines for sedation and seizure prevention, and intravenous fluids for prevention of rhabdomyolysis.[10] More serious metabolic and hemodynamic adverse effects may require admission to a medical or intensive care unit. Brief courses of low-dose antipsychotics can be helpful in managing the psychotic symptoms of an excited delirium but prolonged use is discouraged.[11]

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K2/Spice

Synthetic cannabinoids (Spice)

Background

Synthetic cannabinoids, commonly referred to as "Spice" and "K2," act as agonists at the cannabinoid (CB) receptor.[7] These agents are synthesized and then sprayed on dried herbs that may possess their own implicit psychotropic properties. They are often marketed as "incense" and are typically labeled "not for human consumption" in order to circumvent the Controlled Substances Analogues Enforcement Act of the United States.[7] Synthetic cannabinoids were developed by independent laboratories following research

on the development of CB1/CB2 receptor agonists for the treatment of pain and nausea.[7] Similar to marijuana, they are ingested orally or smoked.

Mechanism of action and neurochemical considerations

Cannabinoid agonists vary in conformation and belong to specific structural groups. The most commonly identified analogues belong to the JWH (John W. Huffman), CP (Cyclohexyl Phenol) or HU (Hebrew University) structural groups.[7,12] Whereas THC is only a partial agonist at the CB1 and CB2 receptors, synthetic cannabinoids act as full agonists at these receptors with an affinity up to 800 times that of THC.[12] Cannabinoid receptors play a role in sensory perception and emotional processing of stimuli in the hippocampus, amygdala, and prefrontal cortex via reduction in GABA release and increase in dopamine and glutamate release.[13] In addition to CB receptor agonism, Spice products are often contaminated with Clenbuterol, which drives sympathetic nervous system activation via agonism at β2 adrenergic receptors.[7,13]

COURTESY OF DRUG ENFORCEMENT ADMINISTRATION (DEA)

K2/Spice

Desired effects, toxicities and long-term effects

The desired effects of synthetic cannabinoids closely resemble those of smoked and orally ingested marijuana, including euphoria, relaxation, disinhibition, and altered perception and consciousness.[7,13] Adverse reactions and toxic effects of synthetic cannabinoids result predominantly from activation of central CB receptors and β2 adrenergic receptors. Somatic and autonomic effects related to the cannabinoid toxidrome include nausea, vomiting, diaphoresis, hot flushes, xerostomia, mydriasis, tachycardia, hypertension, and tremors. Neuropsychiatric toxicities include anxiety, mood dysregulation, perceptual disturbances (hallucinations and delusions), memory impairment, sedation or psychomotor agitation, depersonalization, increased sensitivity to sensory stimuli, suicidal ideation, and seizures. Vascular reactivity and dysfunction have been reported in association with synthetic cannabinoid intoxication and is especially concerning in patients with a history of ischemic heart disease.[13] Tachyphylaxis has been described and is thought to be due to the long half-life of many of the synthetic cannabinoids and their active metabolites.[14] Clinical reports of deaths related to Spice intoxication and its complications are on the rise.[13,14]

Long-term Spice users may develop tolerance. Spice related withdrawal effects include sleep disturbances, seizures and cardiac conduction abnormalities with associated palpitations.[15] As with marijuana, there are several reports of new-onset psychosis following synthetic cannabinoid use that persists beyond the initial intoxication phase. Associated symptoms include paranoid and other delusions, disorganized speech and behavior, affective blunting, and waxing and waning psychomotor slowing. These symptoms may require inpatient management and treatment with antipsychotic medication. Thirty percent of these patients remained psychotic after eight months.[13-15] Other neuropsychiatric sequelae include depressed mood, neurovegetative dysfunction, and suicidal ideation.

Available evidence suggests that prolonged use of synthetic cannabinoids is more strongly associated with persistent psychosis than marijuana. This may be due to the higher affinity of these agents at CB1 and CB2 receptors, dose and potency variation of the active compounds found in synthetic cannabinoids, and the fact that natural cannabis contains cannabidiol, a compound with antipsychotic properties.[16,17]

Diagnostic and therapeutic considerations

Liquid gas chromatography tandem mass spectrometry (LC-MS/MS) and matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDY-TOF) are able to detect synthetic cannabinoids and their metabolites in urine.[13] Like bath salts, testing for synthetic cannabinoids requires use of specialty reference labs with related high costs and delays in reporting of results. There are no published guidelines for the management of the synthetic cannabinoid toxidrome but current recommendations include supportive care, provision of a low-stimulation environments, and use of benzodiazepines for anxiety and sedation.[7,13]

Salvia

Background

Unlike bath salts and synthetic cannabinoids, salvia (*salvia divinorum*) is a naturally occurring herb from the mint family that has been used in Mexico for centuries for its psychogenic effects.[18] Recreational use of salvia has surged over the last decade in the United States and Europe owing to its low cost, ease of purchase online, and a lack of legislation controlling its access and use. Salvia is most commonly smoked but can also be chewed with resulting mucosal absorption.[18]

Mechanism of action and neurochemical considerations

Salvinorin A has been identified as the active chemical responsible for salvia's clinical effects.[18] Salvinorin A is a diterpene compound with highly selective kappa opioid receptor agonist properties resulting in hallucinations, diuresis,

mood improvement and spinal analgesia. In contrast to μ opioid receptor agonists, diterpenes are not associated with respiratory depression. The kappa receptor has been extensively researched for its antidepressant and anxiolytic properties, making it unclear why salvia can produce a paradoxical increase in anxiety.[19,20] The onset and duration of salvia's effects depend upon the route of administration and range from minutes to up to an hour. [20] Salvia is hepatically metabolized by the cytochrome oxidase isoenzyme system and undergoes first pass metabolism, explaining why oral ingestion does not produce neuropsychiatric effects.[20]

Desired effects, toxicities and long-term effects

The desired effects of salvia include a state of "trance" or "reminiscent meditation" that is similar to that produced by lysergic acid diethylamide (LSD), ketamine, and cannabis.[21] The intoxication state is marked by hallucinations, other sensory-perceptual distortions, increased sensitivity to sensory stimuli, synesthesia, out-of-body experiences, and mood elevation.[18,21] Unwanted effects of salvia intoxication include anxiety, dysphoria, confusion, language impairments and fear associated with "bad trips." Symptoms of headaches and drowsiness have been reported to last for several hours after the most recent use.[18] Withdrawal episodes marked by tachycardia and hypertension have been described but these are uncommon.[19] Cases of persistent psychosis in the setting of chronic use have been described and it has been suggested that salvia can unmask or exacerbate preexisting mental illness.[19,21] Cases of salvia addiction have been reported but its prevalence has not been studied.[21]

Diagnostic and therapeutic considerations

Similar to synthetic cannabinoids and bath salts, salvia testing is not part of routine urine drug screens. It, too, can be detected by the use of high-performance liquid chromatography (HPLC) LC–MS/MS or gas chromatography–mass spectrometry (GC–MS) – but with related high cost and delayed result reporting. It remains uncommon for a patient to seek medical care solely for salvia intoxication, but current management recommendations include supportive care treatment with benzodiazepines as indicated for agitation or severe anxiety.[19]

CONCLUSION

Bath salts, synthetic cannabinoids, and salvia are three novel agents in a constantly evolving list of drugs of abuse. Abuse of these substances is particularly worrisome because they are readily available, inexpensive, perceived as harmless by the general public, result in severe somatic and neuropsychiatric toxidromes, and because they are not readily detected by routine drug screening methods. Despite the protean and severe effects of the toxidromes associated with these drugs, medical professionals may be unfamiliar with their presentation and management. The adverse effects of these

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Salvia

and other novel drugs of abuse have been made clear on a local level with a recent report from the Rhode Island Department of Health of 10 deaths from Acetyl-Fentanyl overdose, a fentanyl analogue that is up to five times more potent than heroin. These drugs pose unique challenges to the medical community and regulatory bodies, as advancements in molecular chemistry have paved the way for the continuous development of newer and more potent substances of abuse.

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