Treatment of four psychiatric emergencies in the intensive care unit

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Objectives: **To review the diagnosis and management of four selected psychiatric emergencies in the intensive care unit: agitated delirium, neuroleptic malignant syndrome, serotonin syndrome, and psychiatric medication overdose.**

Data Sources: **Review of relevant medical literature.**

Data Synthesis: **Standardized screening for delirium should be routine. Agitated delirium should be managed with an antipsychotic and, possibly, dexmedetomidine in treatment-refractory cases. Delirium management should also include ensuring a calming environment and adequate pain control, minimizing benzodiazepines and anticholinergics, normalizing the sleep-wake cycle, providing sensory aids as required, and providing early physical and occupational therapy. Neuroleptic malignant syndrome should be treated by discontinuing dopamine blockers, providing supportive therapy, and possibly administering medications (benzodiazepines, dopamine agonists, and/or dantrolene) or electroconvulsive therapy, if indicated. Serotonin syndrome should be treated by discontinuing all serotonergic agents, providing supportive therapy, controlling agitation with benzodiazepines, and possibly administering serotonin$_{2A}$ antagonists. It is often unnecessary to restart psychiatric medications upon which a patient has overdosed in the intensive care unit, though withdrawal syndromes should be prevented, and communication with outpatient prescribers is vital.**

Conclusions: **Understanding the diagnosis and appropriate management of these four psychiatric emergencies is important to provide safe and effective care in the intensive care unit. (Crit Care Med 2012; 40:2662–2670)**

Key Words: delirium; depression; dexmedetomidine; intensive care units; neuroleptic malignant syndrome; mental disorders; posttraumatic stress disorder; serotonin syndrome; overdose

Critical care physicians frequently care for patients with psychiatric emergencies (see Box 1). In this article, we review four selected psychiatric emergencies in the intensive care unit (ICU): agitated delirium, neuroleptic malignant syndrome (NMS), serotonin syndrome, and psychiatric medication overdose. Other neuropsychiatric emergencies are discussed elsewhere (1–3). Early psychiatric consultation, whenever possible, is indicated to assist in each of these psychiatric emergencies.

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DELIRIUM

Delirium has many causes (4). The patient in the case study (Box 1) was delirious due to serotonin toxicity, though other etiologies were considered. In this section, we will focus on the recognition and management of delirium, which affects up to 75% of critically ill patients (5–9).

Recognition

Delirium is defined as a disturbance of consciousness in which patients have a reduced ability to focus, sustain, or shift attention, along with a change in cognition (e.g., memory deficit, disorientation, or language disturbance) or a perceptual disturbance (e.g., visual hallucinations), that is not better accounted for by dementia (10). The onset of delirium occurs within hours to days, and tends to fluctuate throughout the day (10). Simple and reliable instruments have been validated to screen for delirium in the ICU setting, including the Confusion Assessment Method for the ICU (7) and the Intensive Care Delirium Screening Checklist (6). Additional instruments like the Richmond Agitation–Sedation Scale (11) can be used to characterize episodes of delirium in terms of motoric subtypes (12, 13): hyperactive (Richmond Agitation–Sedation Scale +1 to +4 during all assessments), hypoactive (Richmond Agitation–Sedation Scale -3 to 0 during all assessments), or mixed (both positive and negative Richmond Agitation–Sedation Scale scores, over time, during a delirium episode).

Risk Factors

In critically ill patients, the etiology of delirium is often multifactorial. The mnemonic "I WATCH DEATH" may be helpful in thinking systematically about risk factors (Table 1) (3, 4, 14). Other risk factors include immobilization, urinary/fecal retention, and sensory or sleep deprivation (5). Note that some predisposing factors for delirium are not reversible, e.g., old age and preexisting dementia.

Consequences

Delirium is an independent predictor of mortality (9, 15–20) and long-term cognitive impairment (21–23). Delirium is also associated with self-extubation and removal of catheters (24), longer hospital stays (17, 20, 25), and higher medical costs (26).

Delirium may also be associated with long-term psychiatric morbidity (27–31). Critical illness and ICU management are inherently stressful (32), especially when patients are unable to mentally process and communicate effectively. Frightening

Box 1. A psychiatric emergency in the intensive care unit

A 50-yr-old man with a history of bipolar disorder, viral hepatitis, and suicide attempts via overdose was brought to his local emergency room by his wife because he was confused (unable to remember his wife's name), febrile, perspiring excessively, and "stiff." The day prior he had been tremulous and anxious. Upon arrival, he was febrile with increased white blood cell count, transaminases, ammonia, and creatine phosphokinase. No source of infection was identified, and a toxicology screen for common illicit drugs was negative.

The patient was admitted to the intensive care unit (ICU), hydrated vigorously, intubated, and sedated with propofol and haloperidol. His home psychiatric medications (olanzapine, bupropion, and fluoxetine) were held. Brain imaging and cerebrospinal fluid findings were unremarkable. Given clinical worsening, with increased muscle tone, his physicians wondered whether the patient may have neuroleptic malignant syndrome. They administered a single dose of dantrolene, which appeared helpful. The patient was extubated and discharged home after several days. However, he was readmitted to the ICU a week later with a recurrence of his symptoms, and he was transferred to a tertiary medical center.

Upon transfer, he was hyperactive, tremulous, diaphoretic, febrile, and unable to communicate. He exhibited both hyperreflexia and myoclonus. Upon detailed review of his medical records, it became evident that the patient's fluoxetine dose had been doubled shortly before his initial ICU admission (the patient had had worsening depressive symptoms). In between admissions, he had resumed taking fluoxetine. Given his history and acute symptoms, the patient's acute neuropsychiatric state was reformulated as serotonin syndrome. His physicians administered cyproheptadine, and most of his symptoms resolved within 24 hrs. After resolution of his delirium and urinary retention on a general medical ward, he was transferred to the inpatient psychiatric service for treatment of recurrent depression.

psychotic experiences and related memories may be magnified by the administration of catecholamines, which may cross the blood-brain barrier in sepsis and activate the amygdala to produce traumatic memories (33–37). Studies have demonstrated that approximately 25% of ICU survivors have substantial symptoms of posttraumatic stress (27–30, 38, 39) and/or depression (27, 31, 40), sometimes lasting for years. Patients who recalled frightening psychotic experiences in the ICU had substantially more of these symptoms (27, 28, 30, 31).

Treatment and Prevention

The management of acute hyperactive delirium involves treating agitation and psychosis and removing/minimizing risk factors. We highlight measures to treat/prevent delirium beyond standard critical care practice (treating infection, ensuring adequate oxygenation, and managing organ dysfunction and metabolic abnormalities). Note that a prominent hypothesis regarding the pathophysiology of delirium involves deficient cholinergic neurotransmission and excess dopamine neurotransmission (41, 42), and some studies support the use of dopamine blockers (antipsychotics) to prevent delirium (43).

Treat Agitated Delirium and Psychosis. Note that no medications are approved by the Food and Drug Administration to treat delirium. Nevertheless, existing guidelines recommend haloperidol as the medication of choice, based on evidence from case series (44). Advantages of haloperidol include various routes of administration (including the intravenous route for rapid action) and its favorable side-effect profile compared with other antipsychotic drugs commonly used in the ICU setting (44). Although haloperidol can cause dose-dependent electrocardiogram QT interval prolongation, it appears to cause less QT prolongation than other antipsychotics (45). Notably, extrapyramidal symptoms are less common with intravenous haloperidol administration than with oral or intramuscular administration (46, 47). Based on small trials in critically ill patients with delirium (including various motoric subtypes), atypical antipsychotics may be as effective as enteral haloperidol (48–52). To our knowledge, only two studies of antipsychotics for delirium in the ICU have employed a placebo control group (50, 51). First, in a three-arm randomized, blinded feasibility study, neither low-dose haloperidol nor ziprasidone (both administered enterally) significantly outperformed placebo in reducing the time patients spent delirious or comatose (50); however, a larger trial with these same medications is evaluating this question more definitively (ClinicalTrials.gov identifier NCT01211522). Second, in a placebo-controlled trial, quetiapine 50–200 mg every 12 hrs reduced the durations of both delirium and agitation (51); in the trial, intravenous haloperidol was administered, as needed, to patients in both treatment groups—patients in the quetiapine group required fewer days of haloperidol. Beyond the management of agitation, antipsychotics may be used to reduce frightening psychotic symptoms in delirious patients (including those with hypoactive delirium); in order to detect these symptoms, clinicians should have a high index of suspicion and question the patient directly, when possible.

Dexmedetomidine may also have a role in the treatment of agitation. Existing studies have particularly focused on agitation in the setting of ventilator weaning. In one open-label pilot study, 20 patients who could not be successfully weaned because of agitated delirium were randomized to continuous infusions of haloperidol (0.5–2 mg/hr) or dexmedetomidine (0.2–0.7 μg/kg/hr) (53). Dexmedetomidine was associated with a significantly shorter median time

Table 1. Risk factors for delirium ("I WATCH DEATH") (3, 4, 14)

Infection	Central nervous system, systemic
Withdrawal	Alcohol, sedative
Acute metabolic	Electrolyte or acid-base imbalance, liver or kidney failure
Trauma	Brain injury, surgery, severe burns, heat stroke, hypothermia
Central nervous system pathology	Tumor, hematoma, epileptic seizure, hydrocephalus, vasculitis, meningeal carcinomatosis, autoimmune encephalitis
Hypoxia	Respiratory failure, left heart failure, hypotension, anemia, carbon monoxide poisoning
Deficiencies	Vitamin deficiency
Endocrinopathies	Cortisol or glucose dysregulation, hypothyroidism, hyperparathyroidism
Acute vascular	Cerebrovascular accident, shock, arrhythmia, hypertensive encephalopathy
Toxins/drugs	Pesticides, solvents, vitamin intoxication, alcohol or illicit drugs, medications (including γ-aminobutyric acid-ergic agents and anticholinergics)
Heavy metals	Lead, manganese, mercury

to extubation (20 vs. 42 hrs, $p = .016$), as well as a significantly shorter ICU length of stay after study drug commencement (1.5 vs. 6.5 days, $p = .004$) (53). In another open-label, uncontrolled study of 28 patients with agitation during weaning, dexmedetomidine infusion (0.4–1.0 μg/kg/hr) was associated with rapid resolution of agitation (within 6 hrs of infusion commencement) and successful extubation after a median of 70 (interquartile range 28–96) hrs (54). Unfortunately, dexmedetomidine is substantially more expensive than haloperidol, though higher drug costs may be offset by shorter ICU lengths of stay.

Note that administration of medications is not the only intervention that can help agitated delirium. Calm verbal reassurance and reorientation by staff and/or family is also important (4).

Manage Sedation Carefully. Medications that increase γ-amino butyric acid neurotransmission (i.e., benzodiazepines and propofol) are common and important modifiable risk factors for delirium (55–58) and coma (59–62). As needed, bolus dosing and interruption of continuous infusions of sedatives reduce delirium and the duration of mechanical ventilation (59, 63–66) without increasing post-ICU psychological distress (67, 68). Continuous infusions of dexmedetomidine, a non-γ-amino butyric acid-ergic sedative, appear less deliriogenic than benzodiazepine infusions (56, 58). Morphine-only sedation also appears to reduce ICU length of stay (69). Note that, if alcohol or other γ-amino butyric acid-ergic sedative withdrawal is suspected, patients are generally given benzodiazepines more liberally (4).

Minimize Anticholinergics. Anticholinergic drugs are highly deliriogenic (70–73) and should be withheld, when possible, in ICU patients. Of >100 medications commonly prescribed in the elderly (74), those with the most potent anticholinergic properties included dicyclomine, L-hyoscyamine, tolterodine, doxepin, amitriptyline, thioridazine, and clozapine. Those with the next most potent anticholinergic properties included diphenhydramine, oxybutynin, nortriptyline, paroxetine, olanzapine, and chlorpromazine (74). Currently, cholinesterase inhibitors are not indicated for the prevention or treatment of delirium, given negative clinical trial results and potential harm in ICU patients (75–78).

Manage Pain. Inadequately treated pain disrupts sleep and is a risk factor for delirium (79, 80). On the other hand, it is important not to use excessive doses of opioids. Some opioids may be relatively less deliriogenic (e.g., morphine) (57, 81), whereas others appear particularly deliriogenic (e.g., meperidine and tramadol) (81–86).

Promote a More Normal Sleep-Wake Cycle. Disrupted sleep can be both a risk factor for delirium and a manifestation of delirium. Several interventions may be helpful (87). First, promote a quiet environment at night by reducing loud conversations, televisions, unnecessary alarms, and overhead pages (88–90). ICU noise levels often exceed 80 decibels, the threshold associated with sleep disruption (91–94). Second, group together disruptive, but necessary, patient care activities, like clinical assessments, medication administration, wound care, bathing, phlebotomy, transportation, and radiographs (90, 93, 95, 96). Third, minimize sedative agents known to disrupt sleep (e.g., benzodiazepines), and consider alternate methods to address insomnia (i.e., including nondrug measures) (97). Fourth, keep patient rooms dark at night and bright (with daylight) during the daytime (4).

Early Physical Rehabilitation. Providing early physical and occupational therapy in the ICU reduced the duration of delirium and improved physical function in a randomized trial (98). Similarly, an ICU quality improvement project that reduced sedation and facilitated rehabilitation was associated with an increased proportion of ICU days without delirium or coma (99). Conversely, immobility and physical restraints may increase the risk of delirium (100).

Reduce Sensory Deprivation and Orient Patients. Poor visual acuity and hearing impairment are risk factors for delirium (101, 102). Providing eyeglasses and/or hearing aids were part of a multifaceted strategy that reduced delirium in older hospitalized patients (103). Clocks and calendars in patients' rooms (104) and verbal orientation by staff and/or family members (4) may also be helpful.

NEUROLEPTIC MALIGNANT SYNDROME

The features of NMS, serotonin syndrome (SS), and other toxidromes overlap substantially (105, 106). Table 2 illustrates shared and unique features of NMS and SS. The DSM-IV criteria for NMS include severe muscle rigidity, elevated temperature, and other related findings (e.g., diaphoresis, incontinence, decreased level of consciousness, mutism, elevated or labile blood pressure, elevated creatine phosphokinase) developing in association with the use of neuroleptic (i.e., antipsychotic) medication (10). Box 2 lists common antipsychotic medications, as well as other dopamine-blocking drugs (e.g., antinausea medications) that can contribute to NMS. Other adverse drug reactions associated with hyperthermia that should be considered in the differential diagnosis of NMS and SS include adrenergic or anticholinergic toxicity, or uncoupling of oxidative phosphorylation—none of which should be associated with rigidity; malignant hyperthermia (postanesthesia); and baclofen withdrawal (with muscle spasm) (106).

NMS may be increasingly relevant to ICU physicians, given the frequent administration of antipsychotics to critically ill patients for agitated delirium (44, 107). Importantly, several NMS risk factors are common in ICU patients: agitation and use of typical antipsychotics (e.g., haloperidol), often in parenteral form, in higher doses (e.g., 20 mg of haloperidol daily), and in patients who are neuroleptic-naïve (108–111).

Treatment

The correct diagnosis is vital. In particular, the dopamine agonist bromocriptine, given for presumed NMS, can cause or worsen SS. Also, antipsychotics for hyperactive delirium or presumed SS can worsen/prolong NMS (112, 113). No medications are approved by the Food and Drug Administration for the treatment of NMS; recommendations for treatment have been drawn from case series (113). Note that consultation with local poison control centers can be helpful in the management of both NMS and SS (listed at http://www.aapcc.org/dnn/default.aspx).

Discontinue All Dopamine Blockers. It is important to note that antipsychotics are not the only drugs that block dopamine neurotransmission. As shown in Box 2, metoclopramide, prochlorperazine, and promethazine are also dopamine blockers (113).

Provide Supportive Care. Supportive care is the mainstay of treatment for NMS (112, 113). This includes vigorous hydration, attention to electrolyte abnormalities, external cooling for extreme hyperthermia, and managing complications (cardiorespiratory and renal failure, aspiration, and coagulopathies) (112, 113).

Table 2. Characteristics of neuroleptic malignant syndrome and serotonin syndrome (105, 106)

			Identical Features		Overlapping Features			Distinct Features		
Condition	Precipitated by	Onset	Vital Signs	Mucosa	Skin	Mental Status	Muscles	Reflexes	Pupils	Bowel Sounds
Neuroleptic malignant syndrome	Dopamine antagonist	Variable, 1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41°C)	Sialorrhea	Pallor, diaphoresis	Variable: stupor, coma, alert mutism	"Lead-pipe" rigidity in all muscle groups	Hyporeflexia	Normal	Normal or decreased
Serotonin syndrome	Serotonergic drug	Variable, <12 hrs	Hypertension, tachycardia, tachypnea, hyperthermia (>41°C)	Sialorrhea	Diaphoresis	Variable: agitation, coma	Increased tone, especially in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Dilated	Hyperactive

Consider Benzodiazepines for Milder Cases. Benzodiazepines (e.g., lorazepam 1–2 mg intravenously every 4–6 hrs) may ameliorate symptoms in milder cases of NMS, particularly catatonic symptoms like mutism and immobility (113, 114).

Consider Dopaminergic Agents. Bromocriptine (starting at 2.5 mg bid-tid, up to 45 mg/day), amantadine (200–400 mg/day in divided doses), and other enterally administered dopaminergic agents may reverse parkinsonian symptoms (e.g., rigidity) (113), speed recovery, and reduce mortality (115, 116). Note that bromocriptine can precipitate psychosis, hypotension, and vomiting, in which case alternative medications should be considered. Bromocriptine should be continued for 10 days after resolution of NMS, as patients can have a recurrence if it is discontinued prematurely (113).

Consider Dantrolene. The skeletal muscle relaxant dantrolene appears to reduce symptoms, speed recovery, and reduce mortality in patients with NMS who have extreme hyperthermia and rigidity (113, 115, 116). Note that benzodiazepines or dopamine agonists can be administered with dantrolene, but not calcium channel blockers given the risk of cardiovascular collapse (113). Patients can be administered 1.0–2.5 mg/kg intravenously, then 1 mg/kg every 6 hrs if hyperthermia and/or rigidity reduces after the first dose. Side effects can include respiratory and hepatic impairment. If the patient has a good response, dantrolene can be tapered and switched to an oral preparation after the first few days. Dantrolene should be continued for 10 days after resolution of NMS, as patients can have a recurrence if it is withdrawn prematurely (113).

Consider Electroconvulsive Therapy. Electroconvulsive therapy should be considered if supportive care and pharmacotherapy are ineffective after 2 days (113, 117). Electroconvulsive therapy has been effective in pharmacotherapy-resistant cases (117).

SEROTONIN SYNDROME

Though overdoses of serotonergic drugs and the use of serotonergic drug combinations often precede SS (also known as serotonin toxicity), this syndrome can develop in patients taking usual therapeutic doses of serotonergic medications. Combinations of monoamine oxidase inhibitors with other serotonergic drugs are strongly associated with SS (118). Box 3 provides a list of medications and illicit drugs associated with SS, including several drugs that are monoamine oxidase inhibitors and have indications other than depression (e.g., linezolid) (105, 106, 118–120).

Box 2. Drugs associated with neuroleptic malignant syndrome (113)

Typical antipsychotics: pimozide, droperidol, haloperidol, fluphenazine, trifluoperazine, thiothixene, perphenazine, loxapine, molindone, mesoridazine, thioridazine, chlorpromazine

Atypical antipsychotics: clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole

Other dopamine blockers: metoclopramide, prochlorperazine, promethazine

Recognition

SS is characterized by clonus, agitation, diaphoresis, increased muscle tone, elevated temperature, hyperreflexia, and tremor (105, 118, 120). Other symptoms can include confusion, shivering, dilated pupils, hyperactive bowel sounds, tachycardia, and hypertension (105, 118). The most sensitive and specific sign of SS is clonus (121), as highlighted in the Hunter Serotonin Toxicity Criteria (Box 4). Unfortunately, many physicians lack knowledge regarding SS, so the diagnosis is often delayed (122). Thus, it is important for clinicians to be aware of the signs and consider the diagnosis in patients who have been treated with serotonergic drugs.

Treatment

Discontinue Serotonergic Drugs. Some patients' symptoms will resolve within a day of discontinuing serotonergic medications with supportive therapy. However, it is important to note that fluoxetine and its active metabolite have very long half-lives, producing a prolonged syndrome.

Provide Supportive Therapy. Supportive care for SS involves administration of intravenous fluids and normalization of vital signs. Avoid longer-acting

Box 3. Drugs associated with serotonin syndrome (105, 106, 118–120)

Monoamine oxidase inhibitors[a]: tranylcypromine, phenelzine, isocarboxazid, moclobemide, nialamide, iproniazid, clorgiline, and toloxatone (antidepressants); pargyline and selegiline (antiparkinsonian agents); procarbazine (antineoplastic); linezolid and furazolidone (antibiotics); Syrian rue (harmine and harmaline—various uses)
Selective serotonin reuptake inhibitors: fluoxetine, sertraline, paroxetine, fluovoxamine, citalopram, escitalopram
Serotonin–norepinephrine reuptake inhibitors: venlafaxine, duloxetine, milnacipran
Tricyclic and other antidepressants: clomipramine, imipramine, trazodone
"Mood stabilizers": lithium, valproate
Opiates: meperidine, fentanyl, methadone, tramadol, dextromethorphan, dextropropoxyphene, pentazocine
Other antimicrobials: ritonavir
Antiemetics: ondansetron, granisetron, metoclopramide
Antihistamines: chorphenamine, brompheniramine
Antimigraine drugs: "triptans" (controversial) (120)
Supplements/herbal products: L-tryptophan, 5-hydroxytryptophan, *Hypericum perforatum* (St. John's wort), ginseng
Stimulants: amphetamine, 3,4-methylenedioxymethamphetamine ("Ecstasy")
Psychedelics: lysergic acid diethylamide, 5-methoxy-diisopropyltryptamine

[a]Note that the listed monoamine oxidase inhibitors have various uses within and outside of medicine. Thus, we specify their usual indications here.

β-blockers, which can lead to hypotension in patients with autonomic instability (105).

Control Agitation. Agitation in SS can be fairly severe, and sedation with benzodiazepines may be necessary. Benzodiazepines improve survival in animal models of SS, perhaps through a blunting of the hyperadrenergic state (123). Caution is required with the use of physical restraints because persistent struggling against restraints could contribute to worsening lactic acidosis, hyperthermia, and mortality (105, 124).

Consider Serotonin$_{2A}$ Antagonists. Although no medication is approved by the Food and Drug Administration for the treatment of SS, results from case series suggest that patients with moderate-to-severe SS (e.g., tachycardia, hypertension, and hyperthermia) should receive serotonin$_{2A}$ receptor antagonists (105). Cyproheptadine, an antihistamine, is a potent blocker of this receptor at higher doses (12–32 mg in a 24-hr period) (105, 119, 125). A starting dose of 12 mg can be crushed and administered via a nasogastric tube, followed by 2 mg every 2 hrs if symptoms continue, and 4–8 mg q6 hrs for maintenance dosing. In cases in which NMS has been ruled out clinically, the antipsychotic chlorpromazine (e.g., 50–100 mg intramuscular) and atypical antipsychotics may also be considered as alternative serotonin$_{2A}$ antagonists. If activated charcoal has been administered recently, parenteral chlorpromazine may be necessary, as cyproheptadine is not available in parenteral form (120).

Control Autonomic Instability. Patients with hypotension from monoamine oxidase inhibitor interactions with other serotonergic drugs can be treated with low doses of direct-acting sympathetic amines like norepinephrine, phenylephrine, or epinephrine; dopamine should be avoided because of the risk of an exaggerated hemodynamic response (105). In patients who develop hypertension and tachycardia, short-acting agents such as nitroprusside or esmolol are preferred (105).

Control Hyperthermia. Temperature elevations in serotonin syndrome can be severe (>41°C). Antipyretics are not helpful. Patients with high temperatures should be intubated for airway protection to allow deep sedation and neuromuscular blockade with a nondepolarizing agent (105), and active cooling measures should be instituted.

Avoid Bromocriptine and Dantrolene. Bromocriptine can precipitate SS (126); a patient treated with bromocriptine and dantrolene died with signs of worsening SS (127). Notably, dantrolene did not improve survival in an animal model of SS (123).

Box 4. The Hunter Serotonin Toxicity Criteria[a]

In the presence of a serotonergic agent, serotonin toxicity is diagnosed:
If spontaneous clonus[b] is present
Or if inducible[c] or ocular[d] clonus and agitation or diaphoresis are present
Or if inducible or ocular clonus and increased muscle tone and temperature >38°C are present
Or if tremor and hyperreflexia are present

[a]sensitivity 84% and specificity 97% when compared with the "gold standard"—diagnosis by a medical toxicologist (121); [b]alternate involuntary muscular contraction and relaxation in rapid succession; [c]e.g., with rapid dorsiflexion of the ankle; [d]slow continuous lateral eye movements.

MEDICATION OVERDOSE

Patients with psychiatric illnesses are often treated in ICUs after intentional overdoses (128, 129), and ICU physicians must make decisions regarding psychiatric medications, ideally in collaboration with psychiatric consultants. In this section, we outline two principles for patient management.

First, it is often unnecessary to restart psychiatric medications in the critical care setting, i.e., they can be held pending a psychiatric consultation. However,

holding certain psychiatric medications could result in withdrawal. For example, if a patient has been taking a regular dose of a benzodiazepine, it may be necessary to continue it in order to prevent withdrawal symptoms. However, the dose may need to be adjusted based on the clinical state of the patient (e.g., a lower dose if the patient is obtunded or has organ dysfunction affecting drug clearance). Similarly, abruptly stopping serotonin reuptake inhibitors can lead to a distressing withdrawal syndrome that should be avoided by tapering the medicine gradually (130, 131).

Second, it is important to communicate with the physician who prescribed the medication on which the patient overdosed. For example, after a patient has overdosed with a tricyclic antidepressant, a psychiatrist may discontinue this medication and prescribe a medication from an alternative antidepressant class.

CONCLUSIONS

Intensivists often care for patients with psychiatric emergencies. Agitated delirium should be managed with an antipsychotic and, possibly, dexmedetomidine, as well as measures to minimize delirium itself. NMS should be treated by discontinuing dopamine blockers and possibly administering medications (benzodiazepines, dopamine agonists, and/or dantrolene) or electroconvulsive therapy. Serotonin syndrome should be treated by discontinuing all serotonergic agents, controlling agitation with benzodiazepines, and possibly administering serotonin$_{2A}$ antagonists. It is often unnecessary to restart psychiatric medications upon which a patient has overdosed in the ICU, though withdrawal syndromes should be prevented, and communication with outpatient prescribers is vital.

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REFERENCES

1. Krauseneck T, Graz C, Krähenmann O, et al: Psychiatric emergencies on ICU. *Anasthesiol Intensivmed Notfallmed Schmerzther* 2007; 42:10–13
2. Rizos DV, Peritogiannis V, Gkogkos C: Catatonia in the intensive care unit. *Gen Hosp Psychiatry* 2011; 33:e1–e2
3. Irani SR, Vincent A: Autoimmune encephalitis – new awareness, challenging questions. *Discov Med* 2011; 11:449–458
4. Neufeld K, Huberman A, Needham D: Delirium. *In*: Principles and Practice of Hospital Medicine. McKean S, Brotman D, Dressler D, et al (Eds). Illinois, Burr Ridge, McGraw-Hill, 2012, pp 548–558
5. Morandi A, Jackson JC, Ely EW: Delirium in the intensive care unit. *Int Rev Psychiatry* 2009; 21:43–58
6. Bergeron N, Dubois MJ, Dumont M, et al: Intensive Care Delirium Screening Checklist: Evaluation of a new screening tool. *Intensive Care Med* 2001; 27:859–864
7. Ely EW, Inouye SK, Bernard GR, et al: Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; 286:2703–2710
8. Ely EW, Margolin R, Francis J, et al: Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; 29:1370–1379
9. Salluh JI, Soares M, Teles JM, et al; Delirium Epidemiology in Critical Care Study Group: Delirium epidemiology in critical care (DECCA): An international study. *Crit Care* 2010; 14:R210
10. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, DC, American Psychiatric Association, 1994
11. Ely EW, Truman B, Shintani A, et al: Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; 289:2983–2991
12. Peterson JF, Pun BT, Dittus RS, et al: Delirium and its motoric subtypes: A study of 614 critically ill patients. *J Am Geriatr Soc* 2006; 54:479–484
13. Pandharipande P, Cotton BA, Shintani A, et al: Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. *Intensive Care Med* 2007; 33:1726–1731
14. Wise MG: *Delirium*. *In*: Clinical Manual of Psychosomatic Medicine: A Guide to Consultation-Liason Psychiatry. Arlington, VA, American Psychiatric Publishing, 2005, pp 29–48
15. Ely EW, Shintani A, Truman B, et al: Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; 291:1753–1762
16. Lin SM, Liu CY, Wang CH, et al: The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 2004; 32:2254–2259
17. Ouimet S, Kavanagh BP, Gottfried SB, et al: Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med* 2007; 33:66–73
18. Pisani MA, Kong SY, Kasl SV, et al: Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009; 180:1092–1097
19. Shehabi Y, Riker RR, Bokesch PM, et al; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group: Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med* 2010; 38:2311–2318
20. Thomason JW, Shintani A, Peterson JF, et al: Intensive care unit delirium is an independent predictor of longer hospital stay: A prospective analysis of 261 non-ventilated patients. *Crit Care* 2005; 9:R375–R381
21. Jackson JC, Gordon SM, Hart RP, et al: The association between delirium and cognitive decline: A review of the empirical literature. *Neuropsychol Rev* 2004; 14:87–98
22. Girard TD, Jackson JC, Pandharipande PP, et al: Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; 38:1513–1520
23. van den Boogaard M, Schoonhoven L, Evers AWM, et al: Delirium in critically ill patients: Impact on long-term quality of life and cognitive functioning. *Crit Care Med* 2012; 40:112–118
24. Dubois MJ, Bergeron N, Dumont M, et al: Delirium in an intensive care unit: A study of risk factors. *Intensive Care Med* 2001; 27:1297–1304
25. Ely EW, Siegel MD, Inouye SK: Delirium in the intensive care unit: An under-recognized syndrome of organ dysfunction. *Semin Respir Crit Care Med* 2001; 22:115–126
26. Milbrandt EB, Deppen S, Harrison PL, et al: Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004; 32:955–962
27. Davydow DS, Desai SV, Needham DM, et al: Psychiatric morbidity in survivors of the acute respiratory distress syndrome: A systematic review. *Psychosom Med* 2008; 70:512–519
28. Davydow DS, Gifford JM, Desai SV, et al: Posttraumatic stress disorder in general intensive care unit survivors: A systematic review. *Gen Hosp Psychiatry* 2008; 30:421–434
29. Bienvenu OJ, Gould NF, Mason ST, et al: Anxiety disorders prevention: Overview and focus on post-traumatic stress disorder. *Minerva Psichiatr* 2009; 50:265–275
30. Bienvenu OJ, Neufeld KJ: Post-traumatic stress disorder in medical settings: Focus on the critically ill. *Curr Psychiatry Rep* 2011; 13:3–9
31. Davydow DS, Gifford JM, Desai SV, et al: Depression in general intensive care unit survivors: A systematic review. *Intensive Care Med* 2009; 35:796–809
32. Skirrow P, Jones C, Griffiths RD, et al: Intensive care: Easing the trauma. *Psychologist* 2001; 14:640–642

33. Sharshar T, Hopkinson NS, Orlikowski D, et al: Science review: The brain in sepsis–culprit and victim. *Crit Care* 2005; 9:37–44
34. Ebersoldt M, Sharshar T, Annane D: Sepsis-associated delirium. *Intensive Care Med* 2007; 33:941–950
35. Siami S, Annane D, Sharshar T: The encephalopathy in sepsis. *Crit Care Clin* 2008; 24:67–82, viii
36. Ekström-Jodal B, Häggendal J, Larsson LE, et al: Cerebral hemodynamics, oxygen uptake and cerebral arteriovenous differences of catecholamines following E. coli endotoxin in dogs. *Acta Anaesthesiol Scand* 1982; 26:446–452
37. Ekström-Jodal B, Larsson LE: Effects of dopamine of cerebral circulation and oxygen metabolism in endotoxic shock: An experimental study in dogs. *Crit Care Med* 1982; 10:375–377
38. Jackson JC, Hart RP, Gordon SM, et al: Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: Assessing the magnitude of the problem. *Crit Care* 2007; 11:R27
39. Griffiths J, Fortune G, Barber V, et al: The prevalence of post traumatic stress disorder in survivors of ICU treatment: A systematic review. *Intensive Care Med* 2007; 33:1506–1518
40. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, et al: Depressive symptoms and impaired physical function after acute lung injury: A 2-year longitudinal study. *Am J Respir Crit Care Med* 2012; 185:517–524
41. Flacker JM, Lipsitz LA: Neural mechanisms of delirium: Current hypotheses and evolving concepts. *J Gerontol A Biol Sci Med Sci* 1999; 54:B239–B246
42. Steiner LA: Postoperative delirium. Part 1: Pathophysiology and risk factors. *Eur J Anaesthesiol* 2011; 28:628–636
43. Steiner LA: Postoperative delirium. part 2: Detection, prevention and treatment. *Eur J Anaesthesiol* 2011; 28:723–732
44. Jacobi J, Fraser GL, Coursin DB, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30:119–141
45. Glassman AH, Bigger JT Jr: Antipsychotic drugs: Prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 2001; 158:1774–1782
46. Ayd FJ Jr: Haloperidol update: 1975. *Proc R Soc Med* 1976; 69(Suppl 1):14–22
47. Altamura AC, Sassella F, Santini A, et al: Intramuscular preparations of antipsychotics: Uses and relevance in clinical practice. *Drugs* 2003; 63:493–512
48. Skrobik YK, Bergeron N, Dumont M, et al: Olanzapine vs haloperidol: Treating delirium in a critical care setting. *Intensive Care Med* 2004; 30:444–449
49. Han CS, Kim YK: A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics* 2004; 45:297–301
50. Girard TD, Pandharipande PP, Carson SS, et al; MIND Trial Investigators: Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial. *Crit Care Med* 2010; 38:428–437
51. Devlin JW, Roberts RJ, Fong JJ, et al: Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010; 38:419–427
52. Wan RY, Kasliwal M, McKenzie CA, et al: Quetiapine in refractory hyperactive and mixed intensive care delirium: A case series. *Crit Care* 2011; 15:R159
53. Reade MC, O'Sullivan K, Bates S, et al: Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: A randomised open-label trial. *Crit Care* 2009; 13:R75
54. Shehabi Y, Nakae H, Hammond N, et al: The effect of dexmedetomidine on agitation during weaning of mechanical ventilation in critically ill patients. *Anaesth Intensive Care* 2010; 38:82–90
55. Pandharipande P, Shintani A, Peterson J, et al: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; 104:21–26
56. Pandharipande PP, Pun BT, Herr DL, et al: Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA* 2007; 298:2644–2653
57. Pandharipande P, Cotton BA, Shintani A, et al: Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008; 65:34–41
58. Riker RR, Shehabi Y, Bokesch PM, et al; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group: Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA* 2009; 301:489–499
59. Kollef MH, Levy NT, Ahrens TS, et al: The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; 114:541–548
60. Weinert CR, Calvin AD: Epidemiology of sedation and sedation adequacy for mechanically ventilated patients in a medical and surgical intensive care unit. *Crit Care Med* 2007; 35:393–401
61. Payen JF, Chanques G, Mantz J, et al: Current practices in sedation and analgesia for mechanically ventilated critically ill patients: A prospective multicenter patient-based study. *Anesthesiology* 2007; 106:687–695
62. Arroliga AC, Thompson BT, Ancukiewicz M, et al; Acute Respiratory Distress Syndrome Network: Use of sedatives, opioids, and neuromuscular blocking agents in patients with acute lung injury and acute respiratory distress syndrome. *Crit Care Med* 2008; 36:1083–1088
63. Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27:2609–2615
64. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; 342:1471–1477
65. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomised controlled trial. *Lancet* 2008; 371:126–134
66. Needham DM, Korupolu R, Zanni JM, et al: Early physical medicine and rehabilitation for patients with acute respiratory failure: A quality improvement project. *Arch Phys Med Rehabil* 2010; 91:536–542
67. Kress JP, Gehlbach B, Lacy M, et al: The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med* 2003; 168:1457–1461
68. Jackson JC, Girard TD, Gordon SM, et al: Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. *Am J Respir Crit Care Med* 2010; 182:183–191
69. Strøm T, Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. *Lancet* 2010; 375:475–480
70. Tune LE, Damlouji NF, Holland A, et al: Association of postoperative delirium with raised serum levels of anticholinergic drugs. *Lancet* 1981; 2:651–653
71. Han L, McCusker J, Cole M, et al: Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001; 161:1099–1105
72. Flacker JM, Cummings V, Mach JR Jr, et al: The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatry* 1998; 6:31–41
73. Gerretsen P, Pollock BG: Drugs with anticholinergic properties: A current perspective on use and safety. *Expert Opin Drug Saf* 2011; 10:751–765
74. Chew ML, Mulsant BH, Pollock BG, et al: Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc* 2008; 56:1333–1341
75. Liptzin B, Laki A, Garb JL, et al: Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry* 2005; 13:1100–1106

76. Sampson EL, Raven PR, Ndhlovu PN, et al: A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry* 2007; 22:343–349
77. Gamberini M, Bolliger D, Lurati Buse GA, et al: Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery–a randomized controlled trial. *Crit Care Med* 2009; 37:1762–1768
78. van Eijk MM, Roes KC, Honing ML, et al: Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: A multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010; 376:1829–1837
79. Novaes MA, Aronovich A, Ferraz MB, et al: Stressors in ICU: Patients' evaluation. *Intensive Care Med* 1997; 23:1282–1285
80. Nelson JE, Meier DE, Oei EJ, et al: Self-reported symptom experience of critically ill cancer patients receiving intensive care. *Crit Care Med* 2001; 29:277–282
81. Morrison RS, Magaziner J, Gilbert M, et al: Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* 2003; 58:76–81
82. Eisendrath SJ, Goldman B, Douglas J, et al: Meperidine-induced delirium. *Am J Psychiatry* 1987; 144:1062–1065
83. Marcantonio ER, Juarez G, Goldman L, et al: The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994; 272:1518–1522
84. Adunsky A, Levy R, Heim M, et al: Meperidine analgesia and delirium in aged hip fracture patients. *Arch Gerontol Geriatr* 2002; 35:253–259
85. Künig G, Dätwyler S, Eschen A, et al: Unrecognised long-lasting tramadol-induced delirium in two elderly patients. A case report. *Pharmacopsychiatry* 2006; 39:194–199
86. Brouquet A, Cudennec T, Benoist S, et al: Impaired mobility, ASA status and administration of tramadol are risk factors for postoperative delirium in patients aged 75 years or more after major abdominal surgery. *Ann Surg* 2010; 251:759–765
87. Kamdar BB, Needham DM, Collop NA: Sleep deprivation in critical illness: Its role in physical and psychological recovery. *J Intensive Care Med* 2012; 27:97–111
88. Helton MC, Gordon SH, Nunnery SL: The correlation between sleep deprivation and the intensive care unit syndrome. *Heart Lung* 1980; 9:464–468
89. Kahn DM, Cook TE, Carlisle CC, et al: Identification and modification of environmental noise in an ICU setting. *Chest* 1998; 114:535–540
90. Freedman NS, Kotzer N, Schwab RJ: Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 1999; 159(4 Pt 1):1155–1162
91. Topf M, Davis JE: Critical care unit noise and rapid eye movement (REM) sleep. *Heart Lung* 1993; 22:252–258
92. Freedman NS, Gazendam J, Levan L, et al: Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med* 2001; 163:451–457
93. Gabor JY, Cooper AB, Crombach SA, et al: Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med* 2003; 167:708–715
94. Elliott RM, McKinley SM, Eager D: A pilot study of sound levels in an Australian adult general intensive care unit. *Noise Health* 2010; 12:26–36
95. Olson DM, Borel CO, Laskowitz DT, et al: Quiet time: A nursing intervention to promote sleep in neurocritical care units. *Am J Crit Care* 2001; 10:74–78
96. Tamburri LM, DiBrienza R, Zozula R, et al: Nocturnal care interactions with patients in critical care units. *Am J Crit Care* 2004; 13:102–112
97. Bourne RS, Mills GH: Sleep disruption in critically ill patients–pharmacological considerations. *Anaesthesia* 2004; 59:374–384
98. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet* 2009; 373:1874–1882
99. Needham DM, Korupolu R: Rehabilitation quality improvement in an intensive care unit setting: Implementation of a quality improvement model. *Top Stroke Rehabil* 2010; 17:271–281
100. Inouye SK, Charpentier PA: Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996; 275:852–857
101. Inouye SK, Viscoli CM, Horwitz RI, et al: A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med* 1993; 119:474–481
102. Inouye SK: Predisposing and precipitating factors for delirium in hospitalized older patients. *Dement Geriatr Cogn Disord* 1999; 10:393–400
103. Inouye SK, Bogardus STJr, Charpentier PA, et al: A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999; 340:669–676
104. Marcantonio ER, Flacker JM, Wright RJ, et al: Reducing delirium after hip fracture: A randomized trial. *J Am Geriatr Soc* 2001; 49:516–522
105. Boyer EW, Shannon M: The serotonin syndrome. *N Engl J Med* 2005; 352:1112–1120
106. McAllen KJ, Schwartz DR: Adverse drug reactions resulting in hyperthermia in the intensive care unit. *Crit Care Med* 2010; 38(Suppl 6):S244–S252
107. Seitz DP, Gill SS: Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: Case reports and a review of the literature. *Psychosomatics* 2009; 50:8–15
108. Keck PEJr, Pope HGJr, Cohen BM, et al: Risk factors for neuroleptic malignant syndrome. A case-control study. *Arch Gen Psychiatry* 1989; 46:914–918
109. Berardi D, Amore M, Keck PEJr, et al: Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: A case-control study. *Biol Psychiatry* 1998; 44:748–754
110. Sachdev P, Mason C, Hadzi-Pavlovic D: Case-control study of neuroleptic malignant syndrome. *Am J Psychiatry* 1997; 154:1156–1158
111. Viejo LF, Morales V, Puñal P, et al: Risk factors in neuroleptic malignant syndrome. A case-control study. *Acta Psychiatr Scand* 2003; 107:45–49
112. Bhanushali MJ, Tuite PJ: The evaluation and management of patients with neuroleptic malignant syndrome. *Neurol Clin* 2004; 22:389–411
113. Strawn JR, Keck PE Jr, Caroff SN: Neuroleptic malignant syndrome. *Am J Psychiatry* 2007; 164:870–876
114. Francis A, Chandragiri S, Rizvi S, et al: Is Lorazepam a treatment for neuroleptic malignant syndrome? *CNS Spectr* 2000; 5:54–57
115. Rosenberg MR, Green M: Neuroleptic malignant syndrome. Review of response to therapy. *Arch Intern Med* 1989; 149:1927–1931
116. Sakkas P, Davis JM, Janicak PG, et al: Drug treatment of the neuroleptic malignant syndrome. *Psychopharmacol Bull* 1991; 27:381–384
117. Trollor JN, Sachdev PS: Electroconvulsive treatment of neuroleptic malignant syndrome: A review and report of cases. *Aust N Z J Psychiatry* 1999; 33:650–659
118. Sternbach H: The serotonin syndrome. *Am J Psychiatry* 1991; 148:705–713
119. Gillman PK: The serotonin syndrome and its treatment. *J Psychopharmacol (Oxford)* 1999; 13:100–109
120. Sun-Edelstein C, Tepper SJ, Shapiro RE: Drug-induced serotonin syndrome: A review. *Expert Opin Drug Saf* 2008; 7:587–596
121. Dunkley EJ, Isbister GK, Sibbritt D, et al: The Hunter Serotonin Toxicity Criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *QJM* 2003; 96:635–642
122. Attar-Herzberg D, Apel A, Gang N, et al: The serotonin syndrome: Initial misdiagnosis. *Isr Med Assoc J* 2009; 11:367–370
123. Nisijima K, Shioda K, Yoshino T, et al: Diazepam and chlormethiazole attenuate the development of hyperthermia in an animal model of the serotonin syndrome. *Neurochem Int* 2003; 43:155–164

124. Hick JL, Smith SW, Lynch MT: Metabolic acidosis in restraint-associated cardiac arrest: A case series. *Acad Emerg Med* 1999; 6:239–243
125. Kapur S, Zipursky RB, Jones C, et al: Cyproheptadine: A potent *in vivo* serotonin antagonist. *Am J Psychiatry* 1997; 154:884
126. Snider SR, Hutt C, Stein B, et al: Increase in brain serotonin produced by bromocriptine. *Neurosci Lett* 1975; 1:237–241
127. Kline SS, Mauro LS, Scala-Barnett DM, et al: Serotonin syndrome versus neuroleptic malignant syndrome as a cause of death. *Clin Pharm* 1989; 8:510–514
128. Henderson A, Wright M, Pond SM: Experience with 732 acute overdose patients admitted to an intensive care unit over six years. *Med J Aust* 1993; 158:28–30
129. Novack V, Jotkowitz A, Delgado J, et al: General characteristics of hospitalized patients after deliberate self-poisoning and risk factors for intensive care admission. *Eur J Intern Med* 2006; 17:485–489
130. Schatzberg AF, Haddad P, Kaplan EM, et al: Serotonin reuptake inhibitor discontinuation syndrome: A hypothetical definition. Discontinuation Consensus panel. *J Clin Psychiatry* 1997; 58(Suppl 7):5–10
131. Black K, Shea C, Dursun S, et al: Selective serotonin reuptake inhibitor discontinuation syndrome: Proposed diagnostic criteria. *J Psychiatry Neurosci* 2000; 25:255–261