Chapter from the book *Miscellanea on Encephalopathies*
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1. Introduction

An encephalopathic delirium occurs due to a disturbance of brain function leading to a change in mental status. Fluctuating consciousness, hallucinations, disorientation, and short-term memory deficits are common presentations. This syndrome is more frequent among elderly people and occurs in up to 30% of hospitalized patients. There are many medical conditions that can cause a delirium, including organ failures and electrolyte imbalances, etc. Polypharmacy and/or toxicities increase the risk of developing a confusional state. When considering a delirium diagnosis, a thorough evaluation is mandatory. This includes history taking from patients and their family, a physical examination, and a neurological evaluation. Laboratory investigations include a basic metabolic panel, a complete blood count, liver function tests, a calcium assay, toxicology or plasma drug level screening, thyroid stimulating hormone, urine analysis, and in certain cases, a rapid plasma reagin (RPR) and/or human immunodeficiency viral levels (HIV), etc. A computerized tomography scan of the head or magnetic resonance imaging is obtained in most cases. Early, prompt management of delirium decreases morbidity and mortality.

Patients suffering from certain psychiatric conditions can be misdiagnosed as having an encephalopathy and vice versa. Psychosis is common in many psychiatric disorders and may include auditory hallucinations. Psychoses in confusional states will prompt the search for medical causes. Visual hallucinations are most typically observed in cases of a delirium due to a medical condition (e.g., electrolyte imbalance, brain tumor, toxicities, and/or seizures, etc). Tactile hallucinations, or formications, are a feeling that bugs are crawling under the skin and are common with drug use (e.g., cocaine) or alcohol withdrawal. Olfactory hallucinations are often noted in individuals suffering from seizures or brain disorders. Delirium diagnosis becomes especially challenging in people with history of a psychiatric disorder presenting with a new change in mental status. It is important for physicians to be aware of such disorders and to quickly recognize adverse-events caused by psychotropic medications and/or the occurrence of new onset medical disorders. Diagnosis is especially difficult in chronically ill patients, who are poor historians with inability to communicate coherently. This chapter reviews causes of delirium that are secondary to psychiatric drugs as well as reviewing psychiatric mimickers of delirium.
2. Encephalopathy secondary to psychiatric treatments

There are a vast variety of psychiatric medications available. These include antidepressant drug, anxiolytic agents, antipsychotic medications, and mood stabilizers (e.g., antiepileptic pharmaceuticals and/or lithium). Through different mechanisms of action, these medications can result in causing an acute or chronic encephalopathy. Older versions of the psychopharmaceuticals are the most common offending agents. For example, tricyclic antidepressant drugs are more likely to cause anticholinergic induced delirium as compared to the selective serotonin reuptake inhibitors. Neuroleptic malignant syndrome occurs with higher frequency when utilizing older neuroleptic medications versus experience with the newer generation of antipsychotic agents.

2.1 Medications with anticholinergic effects

There are multiple medications that induce anticholinergic effects that include cognitive dysfunction, decreased concentration, confusion, and memory deficits (see Table-1). Delirium occur especially in elderly persons secondary to anticholinergic side-effects caused by antipsychotic and antidepressant medications. A survey of elderly patients hospitalized with an acute medical illness revealed that a significant number were prescribed antipsychotic agents and experienced a delirium, as compared to those not receiving them (10% versus 0%)³.

Many tricyclic and tetracyclic antidepressant medicines are high in anticholinergic potential. Amitriptyline, protriptyline, doxepin, imipramine, and trimipramine are the most notable. In one study, such antidepressant agents were responsible for causing an acute delirium in 13.6% of patients⁴. The second generation antidepressant medications usually have less anticholinergic side-effects⁵.

Clozapine, chlorpromazine, and thioridazine are the antipsychotic agents that have the most anticholinergic potential for causing a delirium⁶. Olanzapine has a moderate affinity to this receptor⁷; other antipsychotic drugs are less likely to cause encephalopathy due to anticholinergia.

First generation antipsychotic agents and risperidone often can result in parkinsonian signs and symptoms that include resting tremors, shuffling gait, a flat affect, cog-wheel muscular rigidity, and bradykinesia. Benztropine and trihexyphenidyl are frequently co-utilized to medicate this adversity, but particularly in elderly patients adding these medicines can induce a delirium.

2.2 Neuroleptic Malignant Syndrome (NMS)

Antipsychotic medications are prescribed to treat people with psychotic disorders and acute agitation. Haloperidol is frequently used in acute medical settings due to its low anticholinergic effects and wide availability in oral and parenteral forms. Delirium can signify the induction of neuroleptic malignant syndrome by antipsychotic drugs. Other medications with similar properties include metoclopramide and prochlorperazine. Dopamine receptor blockade is hypothesized as the pathology behind NMS, but other etiologies might include sympathetic or adrenal dysregulation. Sudden discontinuation of dopaminergic agonists like bromocriptine can also lead to a similar condition.
# Antidepressant Drugs

**SSRIs**
- fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, & escitalopram

- except paroxetine and fluvoxamine (+)

**Bupropion**

**SNRIs**
- nefazdone, venlafaxine, desvenlafaxine, & duloxetine

**TCAs**
- (tri- & tetracyclic antidepressants)
- amitriptyline
- trimipramine
- doxepine
- clomipramine
- imipramine
- desipramine
- nortriptyline

**MAOIs**
- phenelzine
- tranylcypromine
- isocarboxazid

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# Antipsychotic Drugs
**Low Potency Neuroleptics**
- chlorpromazine
- thioridazine
- mesoridazine

**High Potency Neuroleptics**
- haloperidol
- perphenazine
- fluphenazine
- loxapine
- thiothixene

**2ND Generation Antipsychotic Drugs**
- clozapine
- risperidone
- paliperidone
- olanzapine
- quetiapine
- ziprasidone
- aripiprazole

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Table 1. Anticholinergic Effects of Psychotropic Medications

Neuroleptic malignant syndrome occurs in up to 0.02% of individuals medicated with antipsychotic agents. It was previously thought to be of a higher incidence; however, early detection, cautious neuroleptic dosing, and the introduction of second generation antipsychotic medicines might have contributed to this decrease in frequency. NMS is more common in people with dehydration, agitation, iron deficiency, and in rapid antipsychotic medication increases or high dosage applications. Risk may increase also when antipsychotic medicines are co-prescribed with lithium and in patients with a history of NMS. The onset can be within a week of medication initiation.
Autonomic dysfunction is a prominent part of the presentation. Confusion and muscle stiffness are noted. Laboratory findings include elevated transaminases, aldolase, lactic acid dehydrogenase, leucocytosis, and/or metabolic acidosis. High creatinin phosphokinase induced by rhabdomyolysis might result in kidney failure.

Differentiate this syndrome from central nervous system infections which are associated with headaches, fever and localizing signs. Heatstroke can also present with hyperthermia, tachycardia, and confusion; yet, it is differentiated by findings of dry skin and hypotonia. Serotonin syndrome is related to taking serotonergic agents and evidences muscle tremors rather than stiffness. Malignant hyperthermia is a reaction to anesthetic agents. In the workup always rule out psychiatric cases of malignant catatonia.

NMS varies from a life-threatening situation to a self-limited condition, with 63% of cases taken off of the drug recovering within several days. Parenteral depot medication exposure greatly prolongs the course. Fatalities are observed in up to 10% of patients. Immediate discontinuation of the antipsychotic drug is essential.

2.3 Sedative-hypnotic agents

Benzodiazepines and barbiturates can precipitate delirium. Up to 13.9% of patients presenting with acute encephalopathy due to medication, were caused by benzodiazepine intake. In elderly individuals and/or those with liver disease, medication levels can quickly become toxic causing an encephalopathy, even at normal medication dosages. The longer acting benzodiazepines might have a higher risk of causing delirium as compared to shorter acting variants (relative ratio was 5.4 versus 2.6). Higher dosages are also more likely to cause an encephalopathy than lower ones (relative ratio was 3.3 versus 2.6).

Benzodiazepines are usually indicated as a short-term treatment for anxiety, insomnia, and alcohol withdrawal. Yet, very often these medicines are utilized over the long-term. After prolonged duration use or abuse, sudden dosage taper or discontinuation can lead to severe withdrawal symptoms including convulsions and an encephalopathy. Deaths from benzodiazepine withdrawal occur. Thus, seizure precautions and prompt replacement of the sedative medication is emergently required at dosages that stop seizures and suppress hyperadrenergic withdrawal signs.

Barbiturates are no longer commonly utilized; they are mainly prescribed to treat seizure disorders or alcohol withdrawal delirium, especially since some of them have a long half-life and are inexpensive. Sedative toxicity with psychosis has been reported particularly during medication overdoses. Withdrawal delirium (i.e., delirium tremens) can occur after sudden decreases or discontinuation of barbiturates. Isolated visual hallucinations, without overt toxicity or withdrawal, are reported in adults and children.

2.4 Serotonin syndrome

Serotonin syndrome occurs due to hyperstimulation of the 5-HT1A receptors. Etiologies include taking serotonin precursors or agonists (e.g., buspirone and trazodone), neurotransmitter releasers (e.g., amphetamines), reduced serotonin-reuptake from selective serotonin reuptake inhibitor (SSRI) drugs and related agents, or diminishing serotonin metabolism by taking monoamine oxidase inhibitors (MAOIs). Co-prescribing serotonergic
medicines, as in MAOIs with SSRIs or sumatriptan and related drugs, must be avoided. Drug interaction through inhibitors of cytochrome P450 can lead to inhibition of hepatic degradation of the SSRIs, leading to a high blood levels and toxicity risk\textsuperscript{13}.

Serotonin syndrome is an uncommon side-effect of antidepressant drugs, but it is more likely once utilizing medications with a long half-life (e.g., flouxetine). This adversity usually occurs within the first few days of medication initiation\textsuperscript{13}. Three different levels of the disorder are described\textsuperscript{13}: 1. a mild form with tremors, myoclonus, diaphoresis, and restlessness; 2. a syndrome of impaired consciousness or coma, neurological features of myoclonus, tremors or rigidity, autonomic hyperactivity, or breathing difficulties; and 3. a dangerous, toxic condition with coma, seizures, and fever. Deaths occur in the more severe versions, with brain edema and a coagulopathy. Laboratory findings include elevation of the creatinin kinase, transaminases, and leukocytosis.

2.5 Lithium

Lithium is a salt frequently used to treat bipolar disorders or as an augmenting agent for those who suffer from depression. It is effective for controlling manic symptoms at blood levels of 0.6 to 1.2 μg/ml and for maintenance therapy at 0.3 to 0.6 μg/dl. Lithium toxicity is common in dehydrated individuals (see Table-2). Nephrogenic diabetes insipidus occurs in 10% of treated patients and causes dehydration, possibly precipitating toxicity and an encephalopathy. For people over 65 years-of-age, with impaired renal function and polypharmacy, the risk for this adversity increases by two-fold\textsuperscript{14,15}. When co-prescribed with diuretics (e.g., hydrochlorothiazide), non-steroidal anti-inflammatory drugs (e.g., ibuprofen), and/or angiotensin converting enzyme inhibitors (e.g., captopril), lithium excretion is reduced leading to potential toxicity if dose adjustment is not made\textsuperscript{15}.

Toxic symptoms are generally correlated to serum blood lithium levels. Mild cases occur when concentrations are between 1.5 to 2μg/ml, presenting with gastrointestinal upset, mild tremors, and weakness. With moderate toxicity, concentrations range from 2 to 2.5μg/ml and complaints include tinnitus, muscle twitches, dysarthria, and hyperreflexia manifest. At higher blood levels, severe toxicity includes delirium, seizures, coma, and even death; in these cases, blood concentrations are less well correlated to clinical status. Neurotoxicity with permanent sequelae follows high level intoxication\textsuperscript{15}. Thus, significant toxicity mandates hydration and immediate discontinuation of lithium; hemodialysis maybe required.

<table>
<thead>
<tr>
<th>[1] Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Increased perspiration</td>
</tr>
<tr>
<td>b. Nephrogenic diabetes insipidus</td>
</tr>
</tbody>
</table>

| [2] Impaired renal function-nephritis or renal tubular nephrosis |

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Loop diuretics e.g., hydrochlorothiazide</td>
</tr>
<tr>
<td>b. Angiotensin converting enzyme inhibitor e.g., captopril</td>
</tr>
<tr>
<td>c. Non-steroidal anti-inflammatory drugs e.g., ibuprofen</td>
</tr>
</tbody>
</table>

Table 2. Causes of Lithium Toxicity
There is controversy about the safety of combining lithium with antipsychotic medications; several sporadic cases of encephalopathy have been reported with such combinations\textsuperscript{16}. This might be explained by lithium enhancing dopamine receptor blockade\textsuperscript{17}. Otherwise, co-prescribing leads to a higher concentration of intracellular lithium, in a dose-dependent nature\textsuperscript{16}. One retrospective study documented low encephalopathy rates\textsuperscript{18}. Nevertheless, such combinations remain frequently utilized, effective, and safe.

### 2.6 Medication causing hepatotoxicity

Many psychopharmaceuticals can cause liver damage (see Table-3). Acute hepatic failure is an idiosyncratic reaction to medications and can lead to encephalopathy within weeks of first symptom development. Chronic hepatotoxicity and fibrosis usually occurs with long-term treatment; delirium occurs later in the disease process.

<table>
<thead>
<tr>
<th>ANTIDEPRESSANT DRUGS</th>
<th>SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Selective Norepinephrine Reuptake Inhibitor; MAOI: Monoamine Oxidase Inhibitor.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
</tr>
<tr>
<td>Citalopram</td>
<td>+/-</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>?</td>
</tr>
<tr>
<td>Bupropion</td>
<td>+</td>
</tr>
<tr>
<td>SNRIs</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>+++</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>++</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>+</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>++</td>
</tr>
<tr>
<td>OTHERS</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>?</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>?</td>
</tr>
<tr>
<td>TRI- &amp; TETRACYCLICS</td>
<td></td>
</tr>
<tr>
<td>Clomipramine, Imipramine, Amitriptyline, etc</td>
<td>++/+++</td>
</tr>
<tr>
<td>MAOIs</td>
<td></td>
</tr>
<tr>
<td>Phenelzine, Tranylcypromine</td>
<td>++</td>
</tr>
<tr>
<td>MOOD STABILIZERS</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>+++</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>++</td>
</tr>
<tr>
<td>Divalproex</td>
<td>+++</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>++</td>
</tr>
<tr>
<td>Topiramate</td>
<td>?</td>
</tr>
<tr>
<td>Gabapentine</td>
<td>?</td>
</tr>
<tr>
<td>Lithium</td>
<td>?</td>
</tr>
<tr>
<td>OTHERS</td>
<td></td>
</tr>
<tr>
<td>Pemoline</td>
<td>+++</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>++</td>
</tr>
<tr>
<td>Tacrine</td>
<td>+++</td>
</tr>
</tbody>
</table>

Table 3. Psychiatric Medications and Hepatotoxicity
A prominent example was the selective serotonin-norepinephrine reuptake inhibitor, nefazdone, and it has been withdrawn from the market due to this problem. Other drugs can also result in hepatotoxicity; pemoline and tacrine are major offending agents and are rarely utilized now due to this adverse-event. Antiepileptic/mood stabilizer medicines, too, sometimes can induce liver dysfunction. Carbamazepine and valproate products, like divalproex, may cause hepatic inflammation and an encephalopathy. Hyperammonemia might develop even in the absence of other abnormal liver function tests.

### 2.7 Electrolyte abnormalities

Several psychotropic medications may lead to hyponatremia, including antidepressant and antiepileptic/mood stabilizer drugs. Carbamazepine is a well-established offender. Although the mechanism is unknown, stimulation of the 5-HT2 and 5-HT1c might lead to increased release of antidiuretic hormone (ADH) and water retention at renal tubules. Inhibition of norepinephrine reuptake can also lead to increased ADH through α-adrenergic receptor stimulation.

People with serum sodium concentrations at 125-130 mEq/l would present with gastrointestinal complaints of nausea and vomiting and the neurological symptoms of fatigue, headaches, and muscle cramps. Delirium ensues with levels below 125 mEq/l. At concentrations lower than 120 mEq/l, convulsions, respiratory failure, and death are reported. However, some individuals with chronic hyponatremia might be asymptomatic even at more severely low sodium levels. Laboratory evidence includes lower than normal serum osmolality and increased urine sodium or osmolality.

Hyponatremia can occur just weeks after medication initiation. Selective serotonin reuptake inhibitors may have a greater potential for causing this side-effect compared to other antidepressant drugs (ranging from 0.5-32%)21,22. Patients older than age 65 carry a six-fold increased risk. Female gender, high medication doses, low baseline sodium levels, being underweight, co-treatment with diuretic agents, and smoking tobacco are other risk factors (nicotine stimulates vasopressin causing enhancement of water reabsorption from renal tubules).

### 2.8 Leucopenia, neutropenia and/or agranulocytosis

It is important to note that psychotropic medications have been attributed to leucopenia and in rare cases neutropenia. This can predispose people to infections, septicemia, delirium, and death. Clozapine is the antipsychotic drug most associated with bone marrow suppression and use requires special registry for patients and their physicians. A complete blood cell count with white cell differentials is indicated weekly following drug initiation in the first few weeks; the frequency then can be decreased to every other week. Since agranulocytosis develops usually in the first 18 months of this pharmacotherapy, frequency of blood counts can be decreased to monthly intervals after six months of stability. Nevertheless, bone marrow suppression has been reported years after uncomplicated therapy. Immediate medication discontinuation is mandated in all cases of agranulocytosis.

Antiepileptic drugs also have a risk of causing bone marrow suppression. This is especially true with carbamazepine and valproate products. Other medications only rarely cause this side-effect. In contrast, lithium may induce leucocytosis.
2.9 Electroconvulsive Therapy (ECT)

Electroconvulsive therapy is frequently used to treat patients suffering from depression. Delirium can result from the pre-treatment anesthesia or due to the ECT itself. An ECT-induced delirium occurs in up to 12% of individuals, usually resolving spontaneously within an hour. Assurance and benzodiazepines are used to treat any associated agitation. Older age, comorbid neurological disorders, and rapid discontinuation of benzodiazepines after long-term treatment during an ECT series increases the incidence of delirium. Since continued seizures leading to status epilepticus should be ruled out, many physicians continue electroencephalographic monitoring in the post-convulsive period to detect such ictus. A higher incidence of confusion might follow co-prescribing lithium or dopaminergic agents during ECT.

3. Psychiatric disorders mimicking encephalopathy

3.1 Schizophrenia and schizoaffective disorder

Schizophrenia occurs in up to 1% of the population and usually presents first in the late teens and early twenties. According to the Diagnostic and Statistical Manual for Mental Disorders-fourth edition-revised (DSM-IV-R) criteria, to fit this diagnosis, the individual has to have at least two major symptoms for at least six months: delusions which are false fixed beliefs, hallucinations which are misperception of stimuli by the five senses in the absence of stimulation, disorganization of speech, behavior, and/or thought disorder, catatonia or negative symptoms. The negative symptom profile includes apathy, slow movements, ambivalence, and a blunted affect. Catatonia includes motor hyperactivity or excitability, negativism, mutism, waxy flexibility of limbs, and echolalia or echopraxia.

Only one presenting symptom might be enough to diagnose this disorder if there are at least two voices talking to each other in the patient’s mind, “commentary voices”, and/or if the delusion is bizarre. This is particularly so when premorbid social dysfunction has long proceeded the acute psychotic episode, with compromised interpersonal relationships, oddities in behaviors, and low school performance.

There are five sub-types of schizophrenia. This includes a catatonic type; a disorganized version with disorganization of speech, behavior, or thought process; a paranoid type with delusions; an undifferentiated form which has a mixture of symptoms; and a residual one which is less specific but more chronic. Patients presenting with catatonia or disorganization are the ones most easily misdiagnosed.

History taking, with collateral information from the families helps to differentiate schizophrenia from an encephalopathy. A long history of mental illness and its onset during teenage years are usually prominent in schizophrenia; this psychiatric illness has little variation within the day, is characterized by psychotic relapse, and generally evidences intact cognition. Delirium waxes and wanes over time and evidences confusion, poor memory, and disorientation. Preserved cognition is the best clue to ruling out a delirium. Visual hallucinations occur during delirium, while auditory hallucinations more common to schizophrenia. Schizoaffective disorder is a psychosis with a mood disorder component.
3.2 Depressive disorder and bipolar spectrum

Major depressive disorder affects up to 20% of the population, with a higher prevalence among females. Symptoms include feeling sad or irritable, decrease in energy and interest, change in appetite and weight, sleep problems, guilt, anhedonia, and thoughts of suicide. Four to five symptoms are required for at least a duration of two weeks. This syndrome can be associated with psychoses, disorganization, and/or catatonia. Delusions are usually related to one theme and can include nihilistic themes (e.g., the world is coming to an end) and Cotard syndrome (i.e., feeling one is dead and internal organs are decaying). Thorough history gathering and clinical evaluation usually aids in diagnosis. Antidepressant medication alone may not be adequate in psychotic cases, when the addition of an antipsychotic drug is indicated. Since this syndrome is frequently associated with suicidality, medication overdoses should be considered, especially when confusion or a change of mental status is observed. In cases presenting with tricyclic or tetracyclic antidepressant overdose, cardiac monitoring is mandated. Frequent blood work is required for patients on polypharmacy or clozapine. Liver function monitoring is essential in persons medicated with antiepileptic/mood stabilizer drugs.

Bipolar Disorders occur at a rate of 1% in the general population. This cyclic ailment alternates between depression and mania/hypomania, which is characterized by elated or irritable mood, decreased need for sleep, grandiosity, pressured speech, risk taking behaviors, impulsivity, flight of ideas or racing thoughts, and/or distractibility. Three or four symptoms are needed to confirm this diagnosis. Psychoses can also be observed. “Delirious mania” has been described in individuals presenting initially with grandiosity, excitement, and psychosis. They are disorganized and can become delirious. Such cases have been described frequently in younger populations with catatonia evident. This can be challenging to differentiate from delirium alone, especially in elderly cases. History taking, physical examination, and laboratory investigations are important to reach a sound diagnosis. This illness is characterized by acute onset, history of an affective disorder, mania, and response to bipolar treatment. Overt delirium cases evidence cognitive abnormalities, such as disorientation, and require a medical evaluation to rule out toxicities, electrolyte abnormalities, or organ failures, etc.

3.3 Dementia

This disorder is more common in elderly patients and increases in frequency as the individual ages. It can be multifactorial and includes Alzheimer disease, Lewy body dementia, vascular causes, vitamin deficiency, or even infectious offenders (e.g., syphilis). Individuals or relatives usually complain of gradual memory deterioration, aphasia (impairment in language or speech), apraxia (inability to perform complex movements in presence of normal motor function), and problems with executive function. Dementia has a more constant memory deficit pattern, without a waxing and weaning course. Aside from Lewy body dementia, in which visual hallucinations are common, hallucinations usually occur late in the disease or when comorbid delirium exists. Treatable etiologies such as vitamin deficiency, infectious etiologies, and vascular disease should be detected and promptly managed to prevent irreversible disease progression.
3.4 Alcohol and substance-induced delirium

The American Psychiatric Association manual, the DSM-IV-R, has standardized psychiatric disorders that include delirium due to drugs or alcohol. Encephalopathies can occur in individuals consuming alcohol during two stages: 1. alcohol intoxication with delirium and 2. alcohol withdrawal delirium. There is also an alcohol-induced, persisting amnestic disorder with residual dementia that presents initially in a delirium (with Wernicke’s Korsakoff syndrome). Amphetamine, cannabis, cocaine, hallucinogen, inhalant, opioid, and phencyclidine (PCP) drugs can be related to a delirium. Other substances are associated with disorientation and are categorized under a substance-induced delirium group [e.g., gamma hydroxybutyrate (GHB)].

3.4.1 Alcohol withdrawal / delirium tremens

Alcohol is a very frequently abused substance. A single 12-ounce drink of beer, 4-ounces of wines, or a 1-1.5 ounces of 80-proof of spirits raises the blood alcohol level by 15-20mg/dl, in a 150-pound normal male. It takes 30-90 minutes to reach a peak concentration and in healthy people, a further hour to be metabolized. Detoxification is dependent on alcohol dehydrogenase metabolizing alcohol to acetaldehyde, and aldehyde dehydrogenase converting acetaldehyde into acetic acid. Alcohol intoxication can occur more readily, even with less ethanol consumption, in persons lacking these enzymes, as in some Asian populations. Symptoms of ethanol intoxication are correlated to blood alcohol levels. Alcohol dependency involves a need to increase the amount of alcohol to achieve a past same effect and unsuccessful efforts to diminish use despite the knowledge of its deleterious effects. Social and occupational dysfunction is common.

3.4.1.1 Alcohol intoxication

Toxicity occurs within hours of drinking. At levels of 0.05 mg/dl, disinhibition and disturbed judgment becomes evident in non-addicted persons. Motor function disruption is apparent at concentrations above 0.1%. Confusion and encephalopathy occurs near 0.3%, while coma is often observeder at concentrations above 0.4%. Death is most commonly secondary to respiratory inhibition. Signs of intoxication include slurring of speech, motor clumsiness, nystagmus, impaired cognition with delirium, and respiratory depression. In such circumstances, it may be necessary to rule out intracranial hemorrhage, by obtaining a brain imaging scan of the head.

3.4.1.2 Alcohol withdrawal

In ethanol addicted individuals, a withdrawal syndrome can occur within half a day from the last drink or lower alcohol ingestion depending on the amount consumed, other substances used, patient’s tolerance, hepatic status, and enzymatic activity. Withdrawal is associated with autonomic hyperactivity of vital signs, tremors, sweating, anxiety, decreased sleep, and/or perceptual disturbance (visual or tactile hallucinations). Grand-mal seizures can develop in up to 3% of this population.

Delirium Tremens (DTs) is a life threatening degree of withdrawal. It develops, within days to two weeks in addicted individuals after abrupt abstinence or reduced ethanol consumption. The DTs is characterized by severe withdrawal symptoms, seizures, fever, and a delirium. 

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Thiamine deficiency while metabolizing glucose without vitamin B1 can lead to a **Wernicke Korsakoff syndrome**. Wernicke’s is an acute, sometimes reversible condition, secondary to thiamine deficiency leading to bleeding in the mammillary bodies and related areas. It is characterized by delirium, ataxia, and ophthalmoplegia. Korsakoff is a related disorder presenting with confusion and confabulation. Both can result in a residual dementia.

### 3.4.2 Encephalopathy related to substance use

#### 3.4.2.1 Cannabis

The effects of marijuana usually last for up to three hours; yet, its metabolite, tetrahydrocannabinol, can accumulate in adipose tissue, lasting for a much longer duration. This natural substance may cause a delirium. Chronic use can lead to respiratory epithelial damage, increased risk of infections, autonomic hyperactivity, cognitive deficits, and teratogenicity. Synthetic marijuana is sometimes more common and cheaper than natural cannabis. It may be preferred by those who are monitored for drug abuse intake since it is not detected by regular urine drug screens.

#### 3.4.2.2 Stimulants

**Cocaine**: Several fatal cocaine-induced agitated encephalopathy cases have been reported. Cocaine-associated delirium usually presents with hyperthermia, bizarre behavior, and delirium. It may herald cardiovascular collapse and death.

#### 3.4.2.3 Hallucinogens

**Ecstasy (3,4 methylenedioxymethamphetamine) or MDMA**: Several post-ecstasy ingestion reports of delirium have been described in the literature. This drug is thought to combine the effects of lysergic acid diethylamide (LSD) and amphetamines, leading to higher serotonin and dopamine levels. Intake of this substance leads initially to elevation in mood and increased sociability; while in individuals naïve to the drug, it can lead to anorexia, sweating, and elevated vital signs. Psychosis, confusion, and disorganization are sometimes documented. This is mediated by hyperthermic effects of the drug, resulting in electrolyte imbalance with neurotoxicity that can precipitate seizures.

**Gamma-hydroxybutyrate (GHB)**: This substance is a naturally occurring analog of gamma-aminobutyric acid (GABA). There are two other precursor drugs that are inactive unless metabolized into GHB within the body. Cross tolerance between ethanol and these substances do exist.

**Intoxication** with these short-acting agents can leads to euphoria, disinhibition, respiratory depression, and significant central nervous system depression. Combativeness is observed during such intoxications. Hypotension and/or bradycardia are documented. The toxicity usually resolves within a few hours due to the short half-life of the drug. With medical intervention, fatalities are uncommon.

**Withdrawal** has been reported after drug discontinuation in individuals abusing GHB for long periods. High doses of benzodiazepines are required to treat withdrawal tremors,
seizures, hallucinations, delusions, autonomic hyperactivity, and delirium\textsuperscript{36}. Deaths are reported\textsuperscript{10}. Diagnosis is difficult since GHB is non-detectable by routine drug screening and even with special urine testing it is usually no longer detected 12 hours after ingestion\textsuperscript{10}.

3.4.2.4 Opiates

This group of medication has been linked to hypoactive delirium\textsuperscript{37}. Sedation, sleep disturbances, slowed mentation, and inattention are frequent signs. The mechanism is probably multifactorial; yet, anticholinergic effects of these agents might be prominent. Methadone has unpredictable pharmacokinetics and varies from one person to another. Naltrexone, a long-acting opioid antagonist, has frequently been used for rapid detoxification from opiates and blunts the pleasurable effects of opiates. In rare instances, naltrexone leads to delirium\textsuperscript{38}. Disorientation, psychosis, and poor attention or concentration are documented and followed by evidence for withdrawal that includes mydriasis, diarrhea, lacrimation, muscle aches, abdominal discomfort, piloerection, and yawning.

Dextromethorphan is a frequently used antitussive drug that is a dextrorotatory isomer of codeine. When degraded by the liver, it forms a phencyclidine (PCP)-like substance, dextrorphan\textsuperscript{39}. This over-the-counter preparation is frequently abused, and in high dosage can lead to a delirium with euphoria, autonomic hyperactivity, psychosis, agitation, and violent behavior. Ataxia, dysarthria, and seizures have also been reported. Elderly people are more prone to these ill effects, even at conventional doses\textsuperscript{40}.

3.4.2.5 Others

Nicotine Withdrawal: Sudden discontinuation of smoking tobacco leads to bradycardia, agitation, and irritability. On very rare occasions, a delirium or psychosis is documented after discontinuation of nicotine\textsuperscript{41,42}.

Ketamine: This agent is related to phencyclidine and is utilized as an anesthetic due to its analgesic and amnestic effects. Due to its tendency to cause psychoses with illusions, depersonalization, and even delirium, it is not commonly prescribed, but remains in a research status. Such encephalopathies are thought to be more frequent among females using rapid and/or high drug dosage\textsuperscript{43}.

4. Capacity and competency of the patient to make a decision

In a medical setting it is challenging when an ill patient decides not to proceed with an investigation, procedure, and/or treatment. Yet, imposing a decision on someone is only legitimate in certain situations. Forced interventions against an individual’s stated wishes can only be done if the patient is legally declared not competent or found not to be clinically of decisional capacity.

Competency can only be determined in a judicial setting by a court order. The judge permanently appoints a medical guardian to make all future medical decisions. Arranging this may take several days to weeks, rending it unpractical in emergencies.
A medical team might consult with a psychiatrist for a bedside evaluation to determine whether a patient has the “decisional capacity” to make their own medical decisions. The capacity to make a decision must be specific to a particular procedure or plan at a specific time. Unless the individual is overtly delirious or unable to understand their situation, a thorough evaluation is necessary. Decisional capacity can vary between being present or absent quickly over time or vacillate back and forth. The psychiatrist must collaborate with the treating physician to understand the necessity of a procedure and consequences if it is not done in order to communicate this to the patient during the assessment.

There are several issues that must be documented as to reasons why a person is determined to be non-decisional at specific time. They must understand information about their disease, its prognosis, and the suggested procedure. These individuals must understand their own decision and the reasoning behind it. Patients should comprehend alternatives and be able to choose between them. It is helpful to ask all evaluated persons to repeat back their understandings. To be decisional, the patient must demonstrate acceptance of the pathology diagnosed, the advantages and disadvantages of the proposed intervention, and the pros and cons of refusing the medical recommendations. A limited understanding may render people as non-decisional. For example, someone in a coma is never decisional. The individuals involved should be able to clearly communicate their wishes. Communication usually is in the form of speaking or writing, and it must always reflect good understanding of the clinical circumstances. If the patient’s wishes are inconsistent or unclear, this infers a lack of decisional capacity.

All decisional patients are able to coherently clarify their decision and reasoning. Once found to be non-decisional, relatives or medical surrogates are called upon for making medical decisions. In overt emergencies, physicians may become the surrogate when family or guardians are not available; documented collaboration with colleagues and a hospital medical ethics committee consultation is helpful and provides some legal protection. In non-emergent cases, seek permission from a court to obtain guardianship for the non-decisional patient when surrogate decision makers are not available.

5. References


The book project “Miscellanea on Encephalopathies” aims to cover some of the important aspects of infectious-related encephalopathies, post-transplantation and drug-induced encephalopathies, by transmitting valuable information filtered through the real life clinical and research experience of the authors.

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