Medicinal-Induced Behavior Disorders

Sai Krishna J. Munjampalli, MBBS, Debra E. Davis, MD*

KEYWORDS

• Behavioral • Encephalopathy • Medication • Nervous system • Psychiatric
• Side effects • Toxicity • Withdrawal

KEY POINTS

- The neurobehavioral effects of medications are relatively common and potentially life threatening.
- The nervous system can be affected whether the drug is targeted to treat a brain disorder or not.
- Sometimes the presentation follows a well-known pattern and the toxicity is relatively easy to diagnose.
- Other signs and symptoms may be subtle, not recognized by patients or caregivers, or ignored, leading to prolonged problems and risk of more serious complications.

MEDICATION-INDUCED BEHAVIORAL SIDE EFFECTS

In daily neurology practice, we see patients who present with behavioral changes that may not be explained by the primary diagnosis. Because some of our patients also have psychiatric diagnoses, the practitioner must have an open mind to find the cause of behavioral changes. When the secondary causes are being worked up, a complete list of the medications of each patient should be looked at closely, because medication side effects include behavioral changes. Some medications act as neurotoxins that can cause symptoms and signs along a spectrum that includes mild confusion, attention deficits, mood disturbances, fatigue, cognitive dysfunction, and encephalopathy.[1] Behavioral symptoms may resolve with removal from the exposure. However, depending on the toxin, the dose, and the individual, a single exposure of some toxins can result in permanent deficits. The patient may exhibit insidious symptoms and signs that go unrecognized as being attributed to the exposure and may not manifest until years after exposure begins. Significant recovery can take months or years after removal of the toxin, and recovery may never occur. Almost every group

The authors have nothing to disclose.
Department of Neurology, Louisiana State University Health Sciences Center – Shreveport, 1501 Kings Highway, Shreveport, LA 71103, USA
* Corresponding author.
E-mail address: delli1@lsuhsc.edu

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of medications ranging from simple antihypertensive medications to the more complex antineoplastic/immunomodulatory medications, may cause some form of behavioral effects.[2,3] The central nervous system (CNS) is to some extent protected from toxic exposure by the blood–brain barrier (BBB), but remains vulnerable to many toxins nonetheless. Nonpolar lipid-soluble substances gain easiest access and, once that occurs, neurons are easy targets owing to their high lipid content and high metabolism. White matter can also be easily damaged by the lipophilic toxins.[2]

When a patient presents with behavioral changes, the differential diagnosis is initially very broad, and arriving at the correct diagnosis is often a diagnostic challenge. The importance of taking a good history and performing a comprehensive examination cannot be overemphasized. Medication side effects and drug–drug interactions are often overlooked, partly owing to physician oversight and partly owing to the lack of access to the complete medication list. Reviewing both the current and the past medication list is helpful.

CENTRAL NERVOUS SYSTEM TOXICITY

"That guy has delta MS." The meaning of this phrase is easily understood by medical personnel from the lowest levels of training to the most senior clinicians. Unfortunately, however, as a diagnosis it is about as helpful as saying that a patient is sick. Recognition of the syndrome of CNS toxicity is relatively simple; determining the cause and therefore the appropriate management can be a challenge.

A change in mental status can be thought of as too excited (agitation, mania, hallucinosis, psychosis, and seizure) or too sedated (depression, drowsiness, confusion, obtundation, and coma). These can occur in almost any combination, and may wax and wane. The clinician identifies the type as well as other concomitant neurologic and physical findings to steer the diagnostic exploration. These may include autonomic changes such as blood pressure, pulse rate, cardiac arrhythmia, diaphoresis, and pupillary size; or evidence of global neurologic dysfunction such as ataxia, dysarthria, or tremors. **Table 1** lists the major drug classes that affect consciousness.[4]

Depressed Level of Consciousness Owing to Pharmacologic Agents

Ruha and Levine[4] have published a very detailed discussion of the common toxidromes comprising CNS toxicity. In it, they explain that the sedated patient is reacting to an excess of inhibitory influences, most commonly at GABA, opioid, alpha2-adrenergic, and D2 dopaminergic receptors as well as sodium and potassium ion channels. The GABA-A agonists include benzodiazepines, nonbenzodiazepine sedative–hypnotics, barbiturates, meprobamate, ethanol, and anesthetics. Clues as to which agent has been ingested include the degree of sedation (barbiturates are more potent than sedative hypnotics), respiratory depression (barbiturates and opioids more likely), mild hypotension, bradycardia, or hypothermia (implicating a GABA-A agonist), or alternating agitation/sedation which can suggest the toxic effect of a benzodiazepine. GABA-B antagonists include baclofen and gamma hydroxybutirate (GHB). Baclofen causes a complex combination of excitation (seizures, hyperreflexia, clonus, heart arrhythmia) and sedation (bradycardia and hypothermia). GHB has a short half-life and causes a deep coma, which may last several hours, but from which the patient quickly recovers.[4]

The mu opioid agonists (morphine, codeine, heroin, oxycodone, buprenorphine, methadone, fentanyl, and meperidine) cause a classic opioid toxidrome of CNS and respiratory depression with miosis, with or without mild bradycardia, hypotension, or hypothermia. The effects are reversible with naloxone. Comorbid QT prolongation