Recognizing off target drug effects at the gut and brain

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It is difficult to recognize off-target drug effects, leading to delays in diagnosis and predisposing patients to additional harms. Key components in the formulation of the correct diagnosis include the temporal sequence of events. The sentinel injury may target the gut and brain because of common intermediary metabolites and neuroactive substrates. The description of the complaint may vary among practitioners. The biggest issue in recognizing off target drug effects is to consider the possibility.

Keywords: off target drug effects; neurotoxicity; p-glycoprotein; farnesoid X; bile salt metabolism; pharmacovigilance

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Learning points

(1) Clinicians often face complex decisions regarding off target drug effects, both in diagnosis and treatment. (2) A key factor in the diagnosis of off target drug effects is the temporal relationship between drug introduction and adverse effect. The description of the complaint may vary between practitioners. The sentinel injury may target the gut and brain. (3) Clinicians examining classic neurotoxicity descriptions will recognize common initial complaints that mimic naturally occurring illnesses. Fully described presentations feature overlapping complaints in movement, autonomic function and thought processes. (4) Drug clearance can be destabilized by common iatrogenic events, such as fasting for procedures and new drug introduction. The last drug introduced may not be the actual cause of the adverse event but may have disabled co-administered drug transport mechanisms in other organs. (5) Neurotoxicity may present in ways that the patient is reluctant to disclose, such as panic attacks, compulsion, fervor, changes in sexual ideation. (6) The biggest issue in recognizing off target drug effects is to consider the possibility.

How drugs interfere with bile salt metabolism

Drug metabolism has traditionally been associated with the P450 system [1]. It is becoming increasingly clear that other factors, such as co-administered drugs, age, gender and co-morbid states, also influence the metabolism and tissue distribution of drugs [2]. Drug elimination is an intricate, redundant and collaborative process that utilizes the same elimination pathway as cholesterol and bile [3, 4, 5]. Bile salts are under the tight negative control of Farnesoid X (FXR), a nuclear receptor that activates all three phases of drug metabolism [6-8]. The recognition of the importance of the bile salt pathway to drug metabolism is relatively new [9, 10]. A drug may be introduced to target a specific process, such as blood pressure, but go on to alter the physiologic responses of other drugs in other organs. The introduction of a new drug for hypertension may precipitate the toxicity of a
medication that the patient had been taking for years. In general, the process of eliminating and detoxifying a drug requires phase I cytochromes, phase II metabolizing enzymes and phase III transporters [2].

The most studied efflux transporter at the blood brain barrier, p-glycoprotein, (p-gp) is inhibited by common drugs, such as proton pump inhibitors, cannabidiol and early generation calcium channel blockers [11, 12]. Animal models of p-glycoprotein inhibition have shown that the initial toxic features include lethargy, ataxia, tremor and depression [13]. Cannabidiol, one of four ingredients in marijuana, also influences phase II metabolism and specifically inhibits the CYP P450 isoforms in the 2C and 3A families [14, 15]. A similar issue exists with omeprazole, which affects drug delivery and disposition by changing gastric pH, inducing CYP2C19 and inhibiting p-gp [16-19]. It may not be the individual drug that causes change in patient status, but the effect of a drug on the clearance of other drugs. New drug introduction, dose acceleration, change within drug class or breach in the patient’s clearance capacity can all precipitate adverse drug events [20]. In rapidly changing clinical situations, all of the above components may contribute to patient status [21-23]. Clinicians need to recognize that several widely used drug classes and operative procedures directly target the bile salt, and thus, the drug elimination pathway [24]. TABLE 1.

### Table 1. Current medical trends that alter drug clearance

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Description</th>
<th>Gender</th>
<th>Initial complaint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypharmacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing incidence of surgical manipulation of the biliary tree</td>
<td>Weight loss surgery</td>
<td>M</td>
<td>Abnormal voice projection, hoarseness, difficulty swallowing, trismus, tooth grinding, myoclonus, tics, neck pain</td>
</tr>
<tr>
<td>Specific pharmaceutical targeting of the enterohepatic loop for cardio, diabetes and GI health</td>
<td>HmgCoA reductase inhibitors, (1987) fibrates, thiazolidinediones, retinoids, proton pump inhibitors (1990)</td>
<td>M</td>
<td>Restless leg</td>
</tr>
<tr>
<td>Reduction of hormone replacement therapy at menopause</td>
<td>Increase in non-hormonal drug consumption. Lowered competence of the intestinal component of cytochrome 3A4 in women after menopause</td>
<td>M</td>
<td>Weight loss, athletic performance, anabolic, libido, energy, sleep</td>
</tr>
<tr>
<td>The confounding effects of nutraceutical products on the steroid pathway</td>
<td>Weight loss, athletic performance, anabolic, libido, energy, sleep</td>
<td>M</td>
<td>Often not disclosed in the clinical setting</td>
</tr>
<tr>
<td>Legalization of marijuana and inhibition of p glycoprotein.</td>
<td>Fasting for procedures, introduction of dye, extreme athletic events</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Temporary and often iatrogenic collapse of clearance capacity</td>
<td></td>
<td>M</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Classic descriptions of neurotoxicity: note overlapping movement, orofacial location and autonomic instability in early point of care presentations

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Description</th>
<th>Gender</th>
<th>Initial complaint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical dystonia</td>
<td>Neck, jaw, back spasms that may also involve the eyes, throat and tongue</td>
<td>M</td>
<td>Abnormal voice projection, hoarseness, difficulty swallowing, trismus, tooth grinding, myoclonus, tics, neck pain</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Feelings of internal motor restlessness that can present as tension, nervousness or anxiety</td>
<td>M</td>
<td>TMJ</td>
</tr>
<tr>
<td>Pseudoparkinsons</td>
<td>Seborrhea, slowness, rigidity, tremor, shuffling gait, drooling, flattening of the melolabial crease</td>
<td>M</td>
<td>Restless leg</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Involuntary muscle movements in the lower face and distal extremities.</td>
<td>M</td>
<td>Picking at oneself, taking apart watches and radios, sorting common objects. Consider delusions of parasitosis, cutting, onychophagia, trichotillomania, Morgellon’s disease.</td>
</tr>
<tr>
<td>Punding</td>
<td>Stereotypical motor behavior characterized by an intense fascination with repetitive handling and examination of objects, particular mechanical.</td>
<td>M</td>
<td>Lack of facial expression</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Slowness of movement, autonomic instability, orthostasis, loss of bladder control; 2 types; Parkinson’s type; cerebellar type</td>
<td>M</td>
<td>Chapped lips, restless leg, tics</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>Hyperpyrexia, severe muscular rigidity, bradykinesia, tremor, autonomic instability</td>
<td>M</td>
<td>Dizziness, urinary frequency, postural hypotension, bladder dysfunction, sexual dysfunction</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>Fever, myoclonus, rigidity, hyperreflexia, shivering, autonomic instability</td>
<td>M</td>
<td>Muscle cramps, hypertension, leukocytosis, sweating</td>
</tr>
<tr>
<td>Tics</td>
<td>Motor or behavioral: sudden or stereotyped repetitive movements or vocalizations performed inappropriately at irregular intervals.</td>
<td>M</td>
<td>Blinking, sniffing, yawning, throat clearing</td>
</tr>
</tbody>
</table>

**Initial point of care complaints may be subacute in presentation. Common complaints may include lethargy, depression, hoarseness, gastric reflux, bladder irritability and falling. The failure to differentiate between new disease and off target drug effect not only delays the true diagnosis but predisposes the patient to additional harms.**
Drug reactions can mimic many naturally occurring illnesses [25]. A review of classic drug induced neurotoxic syndromes suggests that there are specific vulnerabilities in the basal ganglia, the autonomic nervous system, and areas related to sleep, anxiety and thought [26]. (TABLE 2) The term pathoclisis was introduced to explain this concept, how certain structures and functions in the neurologic system may be harmed by disease or toxic events [27]. Patients replace normal movement with slowed, spastic, repetitive, and involuntary movements that affect the cervical neck, mouth and gustatory structures [28]. Seen early and interpreted as isolated complaints, initial clinical presentations may present as tooth grinding, temporomandibular joint pain, hoarseness, neck stiffness and pain and gastric reflux. Changes in autonomic function may initially present as gastric reflux, dizziness on standing, falling and bladder frequency [29].

Dopaminergic medications are known to provoke anxiety, sleep disturbance, compulsion, hypersexuality and restlessness [30, 31]. The development of compulsion, such as the loss of control over gambling, alterations in sexual ideation, religious fervor, or craving of illicit substances may not be readily disclosed in the clinical setting and may require special sensitivity and targeted questioning [32, 33]. Patients presenting with early drug induced neurotoxicity syndromes are exposed to a wide variety of medical specialists including neurologists, psychiatrists, primary care providers, gastroenterologists and dentists [34]. The common cause of injury (drug toxicity) is missed because each specialty is focusing on its specific dysfunction rather than the overall pattern [35].

The central and enteric nervous systems utilize common neuroactive metabolites that result from cholesterol oxidation and gut microbiota [36]. Endogenous neuroactive substrates, such as GABA, tryptophan precursors, serotonin and catecholamines originate in bile salt metabolism and function prominently in neural function [37]. Hormones related to satiety and gut innervation are expressed in areas of the brain involved in emotion, memory and reward seeking behavior [38].

All of the p450 cytochromes utilized in drug metabolism are present in the brain, where their main physiologic role may be in metabolizing endogenous neurosteroid substrate [39]. Steroid synthesis in the brain provides diverse functions that impact social, cognitive, physical and emotional functions [40-43].

There are age and gender differences in drug clearance [44]. In general, women take more drugs and have a more positive view of the nutraceutical industry [45, 46]. The reduction in
hormone replacement therapy has directly affected medical consumption, with women now taking multiple other drugs to control menopausal symptoms [47].

**Summary**

The recognition of off target drug effects remains one of the most difficult aspects of clinical medicine. Off target drug effects can mimic many naturally occurring illnesses. Pharmacogenomic testing may prove helpful, but in isolation, does not capture the clinical complexity necessary to recognize adverse drug reactions. Complaints that relate to gut and brain may provide more accurate safety signals, provoking targeted expansion of the clinical history, review of systems and sequence of drug introduction. The recognition of off target drug effects will be improved by combining individual patient clearance characteristics, total drug burden and symptom signals that relate to movement, gut and thought processes. (Figure 1)

**Conflicting interests**

The author has declared that there are no conflicts of interest.

**References**


42. Frye CA. "Neurosteroids' effects and mechanisms for social, cognitive, emotional, and physical functions". Psychoneuroendocrinology 2009; S143-161.


46. Miller, MA. Gender-Based Differences in the Toxicity of Pharmaceuticals—The Food and Drug Administration's Perspective. Int J Toxicol. 2001; 149-152.