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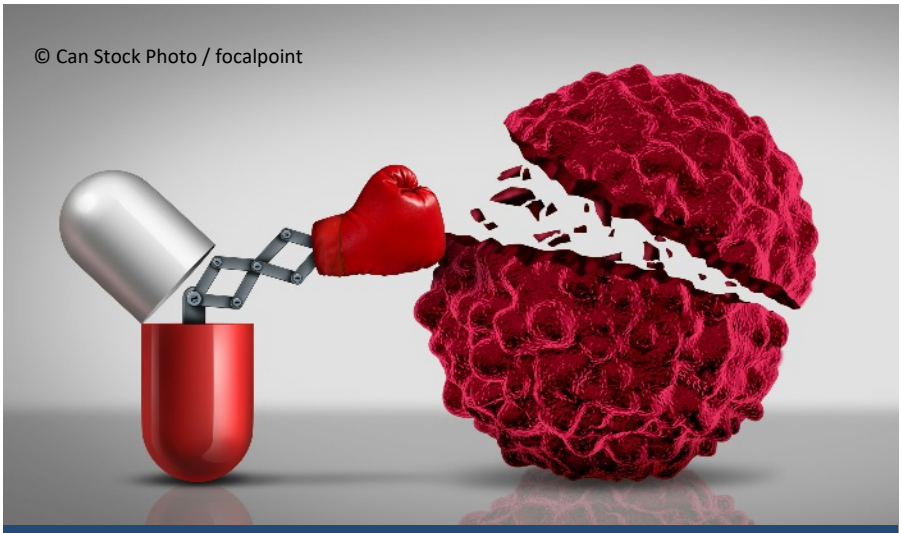

Patient Safety: Aggression, Irritability, and Violence: Drug-induced Behaviors

ABSTRACT: Individuals report many different adverse drug reactions (ADRs) through the United States Food and Drug Administration Adverse Event Reporting System (FAERS) database every year. An overlooked subsection on ADRs involves drug-induced aggression, irritability, and violence. Drug classes most commonly associated with aggressive ADRs are anti-epileptic drugs, antidepressants, immunomodulatory drugs, and benzodiazepines. Many drugs may cause aggressive behavior though multiple theorized modes of action. Neurotransmitters included involve glutamate, norepinephrine, serotonin, and dopamine. By defining aggression and irritability, identifying medications associated with aggressive behavior, and determining how these medications work, pharmacists and technicians may identify high-risk populations and modify treatment to mediate these symptoms.

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INTRODUCTION

In recent years, the media has reported numerous court cases in which defendants have alleged that their behaviors were drug-induced. Pharmacists and pharmacy technicians often perk up and follow these stories closely since medications are their livelihoods. Sometimes, defendants have become intoxicated by choice and become aggressive or violent. The criminal justice system often views claims of drug-induced aberrant behavior skeptically. In an attempt to reduce the criminal charges, defense attorneys may occasionally argue that a drug or drugs that the defendant consumed caused diminished capacity.[1]

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EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Define aggressive and irritable behavior that may be drug-induced
- Identify medications associated with aggression/irritability
- Classify medications causing aggressive behavior by mechanism of action
- Use consultation points to manage drug-induced aggressive behavior

After participating in this activity pharmacists will be able to:

- Describe aggressive and irritable behaviors that may be drug induced
- Recall common medications that can cause aggression/irritability
- Identify what complementary and alternative medicine can cause aggression/irritability
- Determine when to refer patients to the pharmacist for issues regarding aggressive behavior

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Consider this case: In 2006, former All-Star relief pitcher Jeff Reardon was charged with and prosecuted for robbing a jewelry store. Much of the reporting spoke more to his baseball fame (he was a four-time All-Star recipient and played 16 seasons with the New York Mets, Montreal Expos, Minnesota Twins, Boston Red Sox, Atlanta Braves, Cincinnati Reds, and New York Yankees), discussing the case almost as an aside. Distraught over his 20-year-old son's death, Reardon was taking 12 prescription medications including antidepressants and mood stabilizers. Four psychiatrists testified that the drugs caused Reardon to be emotionally unstable and hostile. The judge found him innocent of the charges.[2,3]

Sometimes, cases like this cause pharmacists and pharmacy technicians to shake their heads and think, "Really?" Sometimes, they make us aware of rare or previously unidentified adverse drug reactions (ADRs). This continuing education activity discusses one such set of ADRs: irritability, aggression, and violence. Its goal is to explain how and when these ADRs may occur and help the pharmacy team identify them. Improving safety for the patient and others is the primary goal when these side effects occur.

Emerging Side Effects: Irritation, Aggression, and Violence

Pharmacists look at therapy history, drug levels, and known side effects. When speaking with patients, we focus on common side effects patients are more likely to experience. Many side effects are rare but reported from individuals during drug trials. In recent years more side effect reporting has come directly from patients via reporting agencies. The United States (U.S.) Food and Drug Administration (FDA) Adverse Event (AE) Reporting System (FAERS) database is a large pharmacovigilance database.[4] It provides post-marketing information on adverse drug reports, medication errors, and product quality complaints. The FDA's analysts then compile and scrutinize this information to determine if changes are needed, like modifying product labeling or restricting distribution.[5]

PAUSE AND PONDER: As you read this CE activity, assess the data and decide for yourself: Are irritability, aggression, and violence side effects or adverse drug reactions for various drug classes?

Patient involvement in ADR reporting is steadily increasing. Among 50 countries in 2014, 44 countries had direct patient reporting systems and patients had submitted 9% of total reports, the rest coming from healthcare professionals.[6] In the European Union, patient reports increased 30% between 2014 and 2015 in its EudrVigilance tracking system (a system similar to FAERS).[7] Event reporting from patients and caregivers provides new information and perspective about medication side effects. These reports are often detailed, look at total body effect, and describe side effect's severity and impact on daily life. Health care professional reports frequently do not contain as much information.[8] Many side effects that patients report to FAERS are subjective, suggesting that the agent causes obscure side effects that may have been overlooked in the drug approval process.[4]

Technician Talk: Side Effect or Adverse Drug Reaction?

Healthcare providers tend to use the terms side effect and adverse drug reaction interchangeably. Medical editors debate the proper terminology all the time. The language of side effects is the purview of pharmacovigilance (the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of undesired effects with pharmaceutical products). In general, this is how to differentiate ADRs from side effect:

An **adverse drug reaction** is an unintended and undesired reaction to a medicine given at the correct dose. In general, ADRs are unexpected.

- Adverse drug reactions occur when the drug is initiated, or when the patient discontinues the medication.
- ADRs may be systemic or limited to a specific organ.
- ADRs occur most often in the skin as pruritis (itching), rashes, swelling, or blisters.
- Anaphylaxis is a life-threatening allergic ADR.

A **side effect** is a result of drug or other therapy in addition to or in extension of the desired therapeutic effect that is usually but not necessarily undesirable. Side effects can be expected.

- Side effects are natural consequences of the chemical reactions that take place between the drug and the body. Side effects tend to be mild and often, self-resolving.
- If a hypertensive patient starts an antihypertensive and develops low blood pressure, that's a side effect.
- If a patient taking an anticoagulant hemorrhages, the hemorrhage is a side effect (it could be expected), but it is so serious that it moves into the realm of the more serious **adverse effect**. Adverse effects are serious and may require treatment or drug discontinuation.

Understanding side effects and learning to manage them is an important focus of the pharmaceutical industry. A frequently overlooked side effect is aggressive behaviors: presence of acute/unexpected irritability, agitation, or aggression. A sudden change in mood or behavior can be a shock to some patients—more so if it occurs after taking a medication meant to help.

The FDA wants patients to know when these ADRs are possible. For example, the FDA directed the manufacturer to change the labeling post-marketing on a well-known medication, montelukast (Singulair), to include neuropsychiatric events (symptoms attributed to effects originating from the CNS), including restlessness, agitation, irritability, aggressive behavior, or hostility.[9] By maintaining awareness of behavioral side effects associated with this and other medications, pharmacists and technicians can educate patients on how to recognize and manage these changes.

Defining Terms

How do we define aggression? Aggression could be considered an intent to harm self, an object, or an individual. Researchers in 2007 defined this intent to harm as "overt motor behavior enacted with the intent to do harm or injury to a person or object, with the expectation that harm will occur."[10] Other experts have described aggression previously as threatening, hostile, or violent behavior out of proportion with the level of perceived provocation that induced the behavior. An example could be a patient breaking a plate because it hadn't been washed well, or throwing a prescription vial back at a staff member for filling the medication as generic rather than brand. An outburst's classification as aggressive depends largely on the specific situation, however, so these definitions are fluid.[11]

Agitation is often defined as an episode of intense emotional arousal and motor restlessness. It is characterized by verbal, vocal, or motor activity—although agitated individuals do not necessarily direct their actions at any specific person or thing like individuals who are aggressive do.[12]

Irritability is similarly difficult to describe and define. Many definitions and mental health diagnoses like major depressive disorder and generalized anxiety disorder indicate that irritability is a symptom. Experts describe five components of irritability[11]:

- A heightened or excessive sensitivity to external stimuli
- A negative affective state
- A state of physical and psychological tension that may escalate suddenly and rapidly
- Reduced control over temper, propensity to anger, annoyance, or impatience
- Irascible verbal or behavior outbursts, or even explosive behavior.

Thus, irritability presents causing a person to lose his or her temper because of a certain extreme sensitivity to stimuli outside the person's control.[12]

PAUSE AND PONDER: Thinking back to montelukast—what other medications cause aggressive behaviors as a side effect?

MEDICATION ANALYSIS

Many pharmacists and physicians use Lexicomp to glean information about medications—indications, patient guidelines, and most importantly side effects. One of its features is the ability to search by drug reports—one can look under the "More clinical tools" drop-down and click drug reports. Users can search the database by adverse reaction, indication, and contraindication. A preliminary search of adverse reactions indicates approximately 49 drugs are associated with drug-induced aggression or irritability. Many of these medications may change neurochemical balance and therefore behavior. Other medications on the list affect hormone levels. For example, testosterone and progesterone have often been associated with mood or behavior changes, especially at high doses.[13]

Sixteen of the 49 drugs are in the list of the 100 most commonly used medications of 2019.[14] **Table 1** on page 4 lists drugs on this list associated with aggression or irritability in order from the most often prescribed to least often prescribed (although prescribers use all of these drugs quite often). Using LexiComp as the primary source of side effects has its limitations, but doing so identified trends that have been verified in the professional literature.

Among all medications (not just the most common), some are closely associated with aggression/anger/irritability. **Figure 1** summarizes the 10 drugs with the closest association to aggression and irritability. Let's examine these 10 drugs individually and look for trends.

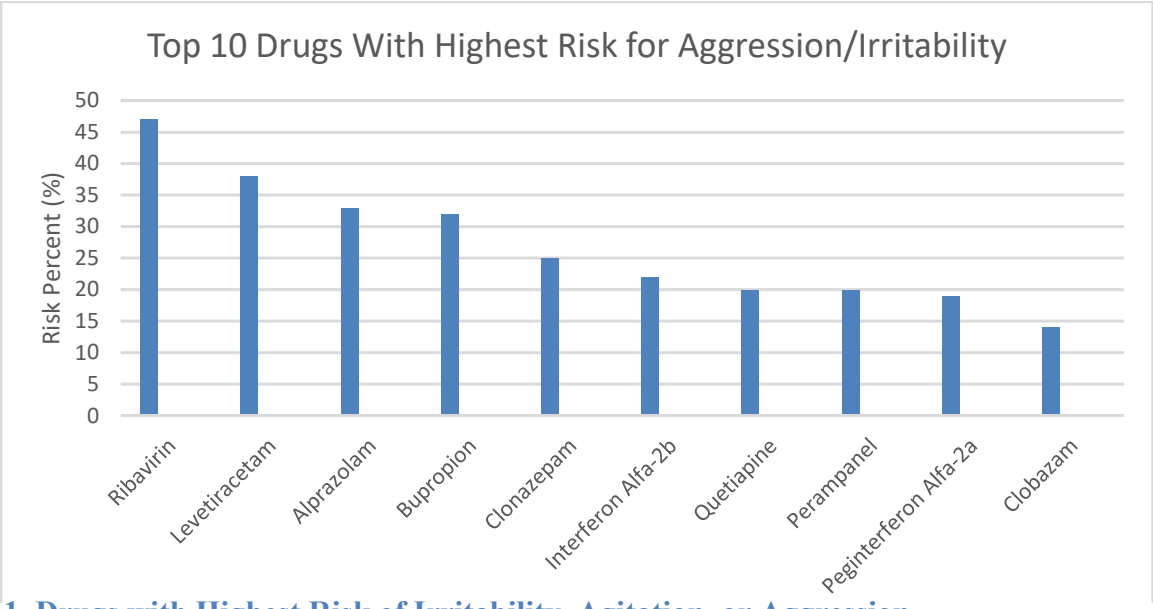

Figure 1. Drugs with Highest Risk of Irritability, Agitation, or Aggression

Table 1. Drugs Among Top 100 that May Cause Irritability, Agitation, or Aggression[15-31]

Medication	Risk	Notes of Interest
Sertraline	8%	Sertraline's patient information advises patients to contact the prescriber if they feel agitated, restless, angry, or irritable or are more inclined to act on dangerous impulses
Alprazolam	33%	Alprazolam's patient information advises patients to contact their doctor right away if they have abnormal thinking
Montelukast	2%	Montelukast's drug monograph suggests that patients and prescribers should be alert for neuropsychiatric events
Bupropion	32%	Bupropion's monograph suggests clinical monitoring for suicidal ideation or other indicators of potential for suicidal behavior is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioral changes
Clonazepam	25%	Clonazepam's monograph states paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, and vivid dreams
Dextroamphetamine /amphetamine	8%	Adderall's monograph states that although there is no evidence that stimulants cause aggressive behavior or hostility, prescribers should monitor patients beginning treatment for ADHD for aggressive behavior or hostility Amphetamine administration is contraindicated in agitated states
Methylphenidate	11%	Ritalin's monograph states the drug is contraindicated in marked anxiety, tension, and agitation, since it may aggravate these symptoms
Duloxetine	4%	Duloxetine's monograph states that agitation was a commonly observed adverse reaction while treating fibromyalgia
Azithromycin	1%	Azithromycin's monograph lists agitation as a side effect in children taking azithromycin
Oxycodone	5%	Oxycodone's monograph lists psychiatric disorders, including agitation, as occurring infrequently
Lorazepam	1%	Lorazepam's monograph mentions paradoxical reactions (including agitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, and hallucinations)
Fluticasone	3%	Fluticasone's monograph notes that adrenal suppression may occur with chronic and excessive use
Esomeprazole	5%	Esomeprazole's monograph states agitation and confusion were rare post-marketing side effects
Lamotrigine	5%	Lamotrigine's monograph includes irritability as one of the side effects observed in monotherapy treatment
Budesonide	3%	Budesonide's monograph mentions behavioral disturbances in children have been observed
Levetiracetam	38%	Levetiracetam's monograph states in adults with partial onset seizures behavioral symptoms (aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, and irritability) were present

Ribavirin, for hepatitis, is not used as monotherapy but approximately 24% to 47% of patients noticed negative behavioral changes.[14]

Levetiracetam, an anticonvulsant, seems to induce behavioral issues in many children—it's reported in up to 38% of children and adolescents.[14]

Alprazolam, a benzodiazepine used for many mood disorders, causes irritability in approximately 33% of patients.[14]

Bupropion, an antidepressant in the dopamine/norepinephrine reuptake inhibitor category, causes irritability in 2% to 32% of reported cases—nearly one third of all patients.[14]

Clonazepam, a benzodiazepine in the anticonvulsant category, has a history of causing behavioral problems in 25% of patients taking the medication.[14]

Interferon Alfa-2b is an antineoplastic agent, used to treat cancer, and n antiviral. Approximately 22% of patients on this medication experienced some form of irritability.[14]

Quetiapine, a second-generation atypical antipsychotic, has been associated with irritability in 2% to 20% of all patients.[14]

Perampanel is an AMPA glutamate receptor antagonist in the anticonvulsant category. Aggression and irritability occurs in anywhere between 12% to 20% of patients on the medication. These symptoms may be dose dependent.[14]

Peginterferon Alfa-2a, used in treating hepatitis C and hepatitis B, can cause irritability in approximately 19% of adults. It is not specified if rates are similar in children.[14]

Finally, clobazam is a benzodiazepine also in the anticonvulsant category, and approximately 8% to 14% of patients reported feeling or acting on aggressive behavior.[14]

The astute reader may see a pattern emerging. Many drugs that induce irritability or aggression are anticonvulsants or antidepressants. Researchers observing connections between drugs and aggressive behavior see the same pattern.

In the following sections, explanations about the underlying causes of irritability, aggression, and violence are dense with neuropharmacology. Simplifying the language is often difficult, although we have tried to make is as understandable as possible. To summarize neurotransmitter actions and help readers, we have included a crib sheet of sorts in the sidebar.

Connecting the Dots: Anti-Epileptic Drugs

Anti-epileptic drugs (AEDs) are medications used to control nerve conduction. One study focused on levetiracetam, perampanel, and topiramate and their history of causing aggressive behaviors.[32] These side effects may occur weeks, even months, after the start of treatment. Researchers looked into possible mechanisms of action (MOAs) and if the aggressive behavior could be an indirect effect related in any way to the AEDs' clinical efficacy. In other words, they wished to know if aggressive behaviors accompanied the drugs' desired actions or were separate and apart from desired actions.[32]

Levetiracetam is a pyrrolidone derivative developed from piracetam. It prevents pre-synaptic vesicles from attaching to the cell wall and releasing neurotransmitters, therefore preventing neuronal cell signaling. Levetiracetam's other MOAs involve

- increasing gamma-amino-butyric acid (GABA) tissue concentrations,
- reducing glutamate's excitatory action,
- modulating calcium and potassium channels, and
- modulating serotonin and norepinephrine signaling.[32]

Researchers state that many of aggression's culprits exist within the brain. Most notable are steroid hormones—androgens and estrogens—and serotonin, plus its actions on other signaling

SIDEBAR: Crib Sheet on Neurotransmitter Roles in Irritability and Aggression

Neurotransmitter	Association with Increased Aggression/Irritability
Dopamine	• Aggression may trigger dopamine release; dopamine release may trigger aggression • Overabundance of dopamine may decrease receptor density, requiring more dopamine for normal nerve transmission (and possibly causing an increased propensity to aggression)
GABA	• Low central GABA levels increase aggression • Increasing GABA results in glutamate antagonism and potentially increases aggression/irritability • Steroids may increase the GABA neuron density, increasing sensitivity to GABA and increasing aggression
Glutamate	• Glutamate's effect is complex • Glutamate antagonism increases aggression/irritability
Norepinephrine	• Increasing norepinephrine levels often leads to restlessness, and sometimes aggressive behaviors
Serotonin	• Decreasing central (brain) serotonin levels often leads to restlessness, and sometimes aggressive behaviors

molecules. Increasing serotonin levels generally decreases levels of aggression—aggressiveness and low serotonin turnover in the brain are connected.[33]

One theory that may explain aggressive behaviors that some people develop with levetiracetam is the reduction of excitatory glutamate. Levetiracetam's precursor molecule piracetam does not affect glutamate negatively and does not seem to increase aggressive behavior. Levetiracetam also may inhibit aromatase, the enzyme that converts testosterone to estradiol; patients taking levetiracetam may have higher testosterone levels and reduced estradiol levels.[32]

Excess testosterone was shown to reduce serotonin production, but also increase estradiol levels in rats, and that in turn caused an increase in serotonin receptor expression. Levetiracetam may cause two negative effects on serotonin:

- increased testosterone levels will decrease serotonin production
- decreased estradiol levels reduce the number of serotonin receptors

The bottom line: less serotonin and fewer receptors to process it. Testosterone and progesterone are included in the 49 drugs mentioned above that may cause aggression or irritability.[32]

Perampanel is an add-on medication—taken in addition to another AED—that selectively reduces glutamate transmission, binding to receptors on the receiving neuron to block activity. Like levetiracetam, perampanel reduces glutamate's excitatory action.[32] Topiramate has several MOAs: sodium and calcium channel inhibition, increased GABA-dependent chloride movement, and glutamate/kainite antagonism. The connecting factor in all three AEDs is glutamate antagonism.[32]

Glutamate antagonism generally increases aggression or irritability, but medications' effects on glutamate—and behavior—is is complex. For example, phencyclidine is a recreational drug known as Angel Dust, and is also a glutamate antagonist. However, this compound causes aggression at low doses but not high doses.[32] More information is needed to make any conclusions, but research has already started with mice.[34,35]

Connecting the Dots: Antidepressants

Antidepressants are a broad category of medications, and many appear within the top 100 drugs list. This class of medication as a whole affects neurotransmitter expression. Clinicians prescribe the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) most often. Researchers conducted a review of SSRI and SNRI reports on suicide and aggression during treatment for depression. They found that the odds of children and adolescents experiencing aggressive behavior was about twice as high as it was for adults. Of the medications included in the study, the top three for serious neuropsychiatric events were sertraline, paroxetine, and fluoxetine—all SSRIs.[36]

SSRIs and SNRIs have a delayed onset of action. For two to four weeks after starting the medications, they increase serotonin release that may activate pre-synaptic serotonin receptors, in turn inhibiting serotonin release. Like with levetiracetam and AEDs, reducing serotonin may cause or contribute to aggressive behavior.

Researchers refer to this aggressive behavior in children as Activation Syndrome (AS). AS is an antidepressant side effect consisting of irritability, mania, self-harm, akathisia (inability to remain still), and disinhibition (lack of restraint). AS has been reported to occur in 4% to 65% of children and adolescents taking SSRIs.[37]

A study examined the level of AS that occurred in patients as sertraline was quickly or slowly titrated in comparison to placebo, using weekly surveys conducted by psychologists.[38] The researchers wanted to determine if symptoms associated with AS would slow treatment progression—if the medication was titrated faster, would AS symptoms be at a level so significant as to require halting or decreasing the dose? While children who received actual treatment (not placebo) experienced substantially higher AS symptoms, symptoms appeared highest during the transition from 0 mg/day to 25 mg/day and 50 mg/day to 75 mg/day in both treatment arms. The target dose for both treatment arms was 200 mg/day, and only 31% of patients achieved this dose.[38] This suggests that the change in behavior may not be linked to the speed of titration for younger patients, but could be linked to medication dose. Some studies have also observed this phenomenon—that AS may be linked to SSRI plasma levels.[39]

Much evidence of drug-related aggressive and irritable behavior comes from patient interviews, but researchers prefer more objective measures. In one study, the researchers summarized and evaluated reported acts of violence associated with therapeutic drugs among all serious adverse drug events reported to FAERS from 2004 through 2009. "Acts of violence" in this case

referred to any report containing homicide, physical assault, physical abuse, homicidal-ideation, or violence-related symptom.

The researchers analyzed reports by determining their proportional reporting ratio (PRR).[40] PRR compares the proportion of violent events to all other violent events for all other drugs. If a drug has a PRR of 6, then the number of violent events is six times greater for that drug than all the other drugs combined.[40]

Bupropion has a PRR of 3.9, meaning there were 3.9 times more violence events associated with bupropion than other medications.[40] Unlike SSRIs and SNRIs, bupropion does not affect serotonin reuptake. Bupropion inhibits norepinephrine and dopamine reuptake and has no clinically significant serotonin effect.[41]

Neurochemical studies have examined a possible connection between aggression and dopamine. Rats exposed to aggression show downregulated dopamine receptor density, and acts of aggression/impulsive behavior seem to stimulate dopamine release. This suggests that aggression may serve as a trigger for dopamine release in reward systems (although some experts believe that dopamine release may trigger aggression).[42] Bupropion reduces dopamine reuptake, leading to a flood of available dopamine. This overabundance of dopamine may decrease receptor density, leading to the need for more dopamine release to cause nerve transmission. Aggression, in this theory, would trigger that dopamine release.

Connecting the Dots: Immunomodulatory Drugs

Some other medications causing aggressive behavior have immunomodulatory effects—for example, montelukast. It is a selective leukotriene receptor antagonist, prescribed to manage asthma and allergy symptoms. Its most common adverse events are headaches, abdominal pain, and rash. In a retrospective analysis of all ADRs in people older than one year of age, epidemiologists looked at montelukast's most serious and most often reported ADRs.[43] The authors examined the reporting odds ratio (ROR). The ROR compares the rate of reporting a specific ADR in a drug in comparison to the rate of reporting the same ADR for all other drugs. The greater the ROR, the more times that specific ADR was reported for that drug. Aggression was one of the more frequently reported ADRs found using their global spontaneous reporting database, reported in a total of 1,101 of 17,723 total reports (approximately two of every 25 reports).[43] Of the 1,101 reports of aggression, the ROR for patients under 19 years of age was 29.77%, or roughly one in four. This value is relatively high, pointing toward a strong relationship between the ADR and montelukast.

Researchers theorize that neuropsychiatric symptoms—like agitation—were reported frequently because montelukast may have an effect on blood-brain permeability and modify neurotransmitter production. Recent studies support this theory. Researchers wonder if decreased blood brain barrier permeability modifies the expression of neurotransmitters in such a way that it causes agitation and aggression.[43]

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Connecting the Dots: Benzodiazepines and Anabolic Steroids

Benzodiazepines are often used for their sedating effects. Literature reports that while opposite, or paradoxical, effects are rare, they do occur. Single dose studies emphasize the low prevalence of aggressive reactions, but evidence consistently correlates aggression and benzodiazepine intake in animal and human studies. The mechanism behind the paradoxical reaction is unknown. Researchers suggest that patients may experience aggressive reactions while on benzodiazepines due to interactions with other drugs or pre-existing brain imbalances like learning disabilities or poor impulse control.[44]

The stereotype that taking steroids causes "roid rage" is not at all out of left field. According to some mouse studies conducted in 2009, anabolic steroids alter neuronal firing parameters in aggression-associated regions of the mouse brain.[45] This suggests that steroid exposure changes communication between neurons. Some evidence demonstrates that steroids dramatically increase the density of GABA neurons and influence steroid-induced aggressive behavior.[45]

IMPLICATIONS FOR PHARMACY STAFF

Intervention may be necessary, depending on symptom severity and how it affects quality of life. The first step to intervention is determining the population that is at highest risk (while appreciating that anyone might develop an ADR).

Repeatedly, studies suggest that children are at highest risk of drug-induced aggression. A study examining SSRI treatment and FAERS reports of violence stratified results by sex and age. A statistically significant increased risk of violent crime conviction was found in patients aged 15 to 24, but the risk of conviction was the same across sexes.[46]

Activation Syndrome was described earlier as affecting children only. Children experience more total adverse events, more activation-related adverse events, and are more likely to discontinue antidepressants due to activation-related ADR.[47] The literature estimates that AS occurs in 12% to 13% of children.[48] Clinicians should make note of one issue, however. Historically, asthma symptoms are associated with depression and decreased quality of life. Children may manifest depression as anger or frustration at their current situation or lifestyle. Clinicians and caretakers may misinterpret depression's symptoms as undirected or overexpressed agitation. When children who have asthma develop irritability or aggression, clinicians should screen for depression.[47,48]

Because ADHD and activation symptoms overlap, the risk of activation may be increased in pediatric patients with ADHD. Evidence suggests that stimulant treatment may exacerbate externalizing symptoms (behaviors like physical aggression, disobeying rules, cheating, stealing, and destruction of property) in susceptible individuals. Amphetamine-based stimulants may be uniquely associated with treatment emergent irritability.[49,50] A recent meta-analysis of irritability in stimulant-treated children associated amphetamine derivatives with a significant increase in irritability, but methylphenidate-based medications decreased irritability relative to placebo.[47] Clinicians and parents should monitor children with ADHD closely for behavioral changes.

Often patients do not recognize these symptoms themselves because they are subjective rather than objective behaviors. Speaking to the patient's friends or family (with the patient's permission) can provide insight into changes in the patient's actions. Experts in many fields often suggest using recording tools to improve other areas of health. Patients with uncontrolled blood pressure sometimes keep a diary of heart rate and blood pressure, and patients with diabetes often benefit by keeping a log of calorie intake to modify their insulin regimen. Mental health professionals also encourage the use of personal recording equipment—such as an app or diary. These tools can improve personal insightfulness and help the patient to modify their behavior.

Scales and short tests are used in the field to quickly score or rate patients depending on their presenting symptoms and behaviors. Patients, parents, or healthcare professionals can use the Brief Irritability Test (BITe) (see **Table 2**), a series of 5 questions that assess a person's current irritability, in men or women.[51] It is short and quick, unlike other anger or aggression questionnaires that can be lengthy. A study observed the BITe has minimal conceptual overlap and has a strong internal structure, meaning that the questions do not repeat and remain consistent.[51] If administered before treatment starts, this test would establish a baseline irritability level (and prescribers might avoid using medications linked to increased irritability or aggression). It could also identify changes in behavior after starting medications that may cause aggression or irritability.

Table 2. BITe Test[51]

	Never	Rarely	Sometimes	Often	Very Often	Always
1. I have been grumpy.						
2. I have been feeling like I might snap.						
3. Other people have been getting on my nerves.						
4. Things have been bothering me more than they normally do.						
5. I have been feeling irritable.						
Never = 1, Rarely = 2, Sometimes = 3, Often = 4, Very Often = 5, Always = 6 **Total sore = sum of all questions**						

Table 3. The FINISH Mnemonic for Antidepressant Discontinuation Syndrome[53]	
Flu-like symptoms	Lethargy, fatigue, headache, achiness, sweating
Insomnia	With vivid dreams or nightmares
Nausea	Sometimes vomiting
Imbalance	Dizziness, vertigo, light-headedness
Sensory disturbances	Sensations of burning, tingling, shocks
Hyperarousal	Anxiety, irritability, agitation, aggression, mania, jerky movement

Pharmacists might recommend that the prescriber stop the medication. However, for many AEDs and antidepressants, this is not the best option. Many of these medications cannot be stopped abruptly, or may be needed for their primary indication. A leading researcher in AED treatment notes, "It is inappropriate to abruptly discontinue any AED because of an increased risk of withdrawal seizures or even status epilepticus. This principle is particularly true for benzodiazepines and barbiturates."[52]

Antidepressants should also be tapered, or they may cause antidepressant discontinuation syndrome. Symptoms are normally mild, but can be a cause of concern for many patients and could happen after stopping any type of antidepressant. **Table 3** lists symptoms following the mnemonic FINISH.[53] Of note, stopping antidepressants or benzodiazepines abruptly because of the unpleasant side effect of anger or aggression could actually worsen the symptom before resolution.

Some medications may be stopped immediately if the side effect is concerning for patients. Montelukast can be started or stopped quickly depending on symptom presentation.

Numerous complementary and alternative medications (CAMs) have been reported to cause irritability and aggression in some patients. A case report described a patient's use of ginkgo biloba in addition to her schizophrenia treatment risperidone in an attempt to improve her concentration and short-term memory. She reported symptoms of agitation and difficulty controlling her anger after taking the antioxidant supplement for approximately one week. She stopped the medication, and her symptoms disappeared. With reintroduction of the supplement one month later, her anger and irritability returned.[54] **Appendix I** lists other CAM and common substances that have been associated with irritability, anger, and aggression (reported as psychosis) in the Natural Medicines Database.[55]

Table 4 lists appropriate actions for pharmacy staff when they suspect or patients ask about irritability, aggression, or violence as a side effect.[56] While medication side effects can be startling for patients, advise them to not abruptly stop their medication without first consulting a doctor or a pharmacist.

PAUSE AND PONDER: What over the counter medications should we monitor for behavioral side effects?

Table 4. Monitoring and Managing Drug-Induced Irritability, Aggression, or Violence[56]

• Recognize that complex antecedents to aggression often involve interaction of diagnosis, medication regimens, and environmental cues
  ◦ In some cases, patients whose symptoms are improving simply feel good enough to misbehave; this is call "release phenomena"
  ◦ In some cases, patients are manifesting symptoms of depression
• If a patient's aggression or irritability escalate when drug management is implemented (or de-escalate when the drug is stopped), it is reasonable to suspect the drug
  ◦ Also consider the patient's baseline level of aggression, irritability, and personality when evaluating whether aggression or irritability is drug-induced
  ◦ Avoid medications likely to cause aggression if patient has a baseline of greater aggression, irritability
• If a medication cannot be stopped, provide or refer patients to training that identifies specific ways patients and families can reduce risk (by understanding the propensity towards irritability, avoiding triggers, maintaining a calm milieu, etc.)
• Encourage patients and their caregivers to document behaviors in a diary or tracking log
• Monitoring for adverse events and discontinuing ineffective medications are tasks that busy clinicians may forget, but appropriate for pharmacists and essential for good care
  ◦ Little to no information documents when aggression/irritability side effects might occur; it could begin when treatment starts or emerge much later
  ◦ Advise patients and their families to remain vigilant
• Ask about complementary and alternative product, OTC or sports steroids, or recreational drug use
• When patients must remain on a medication that may cause or contribute to irritability, aggression, or violence, tailor therapy and use the lowest effective dose
• Observe patients and the people who accompany them closely. If the group dynamic is poor, suggest they discuss their communication and interaction style with their primary care provider or a therapist

Changing the medication is another option. Unfortunately, many drugs in the antidepressant category have similar mechanisms of action, and therefore pose the same risk of affecting mood. In a previous study on antidepressant ADRs involving aggression, amitriptyline was associated with the fewest case reports of violence. It is also the only tricyclic antidepressant included in the list, others being SSRIs or SNRIs. Amitriptyline's mechanism of action is poorly understood, but it is thought to inhibit the membrane pump responsible for clearing serotonin and norepinephrine from the synaptic cleft between neurons. Restlessness is listed as one of its side effects, but not irritability, agitation, or aggression.[57] Depending on the side effect's severity, it may be beneficial for some patients to switch to amitriptyline if it does not interact with the patient's other medications taking.

CONCLUSION

While aggression, irritability, and violence may seem like exaggerated ADRs or side effects, they are real issues associated with many known medications. Patients of all ages and sexes have reported these ADRs to their clinicians and pharmacy staff, yet recognition of these effects remains lackluster. The mental health professional is often called upon to evaluate individual acts of aggression in the clinical, forensic, and school setting. Evaluation rarely happens before the act of aggression occurs. Causes and treatment of aggression and violence are poorly understood and understudied throughout all fields; most information is theoretical.[58] By increasing patient and pharmacy staff knowledge of these possible ADRs, recognition and treatment can be accelerated and unacceptable behaviors avoided.

Pharmacy staff can address under-reporting of ADRs effectively. Referring back to the study involving ADR reports submitted by patients and caregivers in the European Union in 2015, the number increased by 30% from the previous year. Although patient reported ADRs continue to rise as reporting systems become more accessible, pharmacy staff should encourage patient participation in reporting so they can make more of an impact on healthcare.

Pharmacists and pharmacy technicians are accessible healthcare providers.[59] Often they are the first healthcare providers to be approached for questions on medication side effects and OTC treatment options. We are uniquely positioned to inform and direct patient care on a level other healthcare providers do not. We know what to look for, how to identify, and how to manage aggressive behaviors. Pharmacists and pharmacy technicians stand to be the best reference possible for patients and caregivers affected by drug-induced aggression, irritability, and violence.

Figure 2. Maximizing the Pharmacy's Role in Monitoring for Behavioral Effects

Best

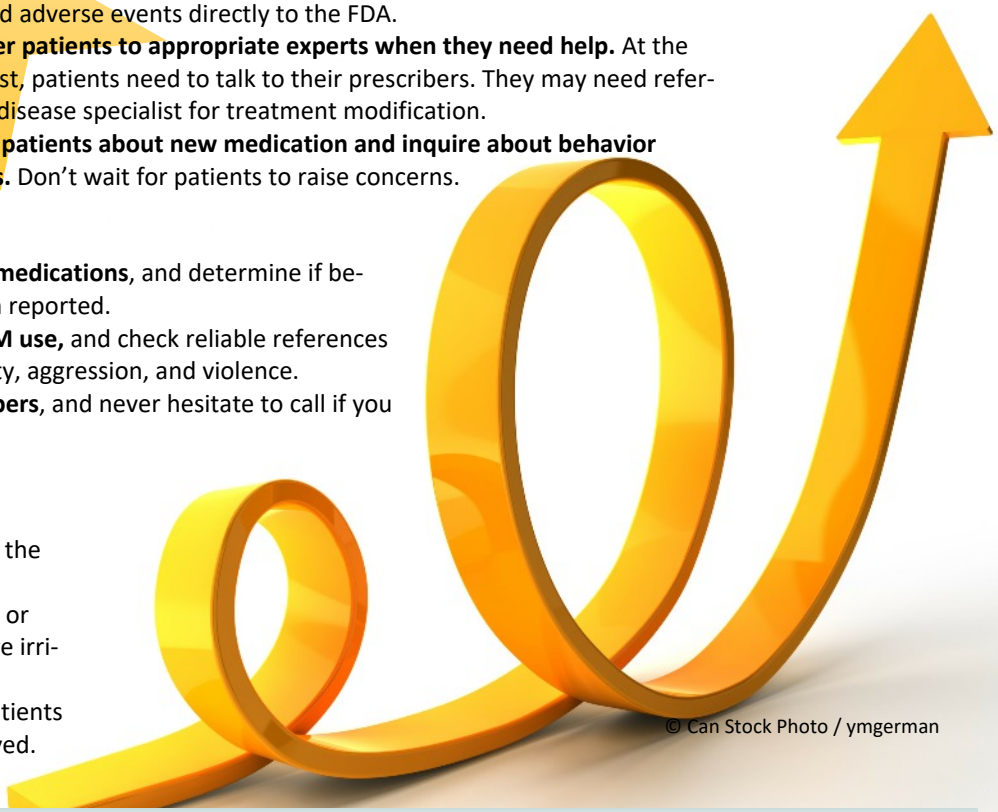
1. **Be COMMUNITY CHAMPIONS.** Encourage patients to report side effects and adverse events directly to the FDA.
2. **Refer patients to appropriate experts when they need help.** At the very least, patients need to talk to their prescribers. They may need referral to a disease specialist for treatment modification.
3. **Ask patients about new medication and inquire about behavior changes.** Don't wait for patients to raise concerns.

Better

1. **Consider the patient's medications**, and determine if behavioral changes have been reported.
2. **Ask about OTC and CAM use,** and check reliable references for information on irritability, aggression, and violence.
3. **Know patients' prescribers**, and never hesitate to call if you have a concern.

Good

1. **Know that many medications** have the potential to alter behavior
2. **Listen** if patients mention that they or someone they interact with seems more irritable or aggressive than normal.
3. **Ask a few questions** about what patients or their friends or relatives have observed.



Appendix 1. CAM and Other Substances Associeted with Aggression/Irritability[55]

CAM Products	Purported Indication	Potential Effect
Angel's Trumpet Devil's Trumpet	○ Recreation: hallucinations and euphoria ○ Medicine: Asthma	Aggressive and Auto-aggressive behavior
Beer/Wine Alcohol, Ethanol, Wine Extract	○ Recreation: lowers inhibitions ○ Medicine: reduce risk of CVD, ischemic stroke, T2D, cognitive decline, AD, dementia, osteoporosis, metabolic syndrome, depression, gallstones/kidney stones, cancer, anxiety, achlorhydria, SLE, URTI, appetite stimulant and Helicobacter pylori infection	Emotional lability, depression and aggression
Belladonna Deadly Nightshade, Devil's Cherries, Devil's Herb, Divale, Dwale, Dwayberry, Great Morel	○ Medicine: ○ Oral: sedative, antispasmodic (asthma and whooping cough), cold/fever remedy, PD, intestinal and biliary colic, IBD, motion sickness ○ Topical: rheumatism, sciatica, neuralgia; psychiatric disorders, hyperkinesis, hyperhidrosis, and hemorrhoids	May lead to psychosis and agitated delirium. In some cases, intake has been a suicide attempt
Betel Nut Areca Nut, Areca Palm, Betel Quid	○ Recreation: central nervous system stimulating ○ Medicine: schizophrenia, glaucoma, mild stimulant, and digestive aid	Psychoactive and anxious behavior
Caffeine methylxanthine, trimethylxanthine	○ Medicine: migraines, headaches, asthma, gallbladder disease, ADHD,OCD, exercise-induced hypoxemia, PD, memory, intermittent claudication, liver cirrhosis, hepatitis C, stroke, post-operative recovery, decreasing pain, exercise-induced muscle soreness, age-related cognitive impairment, neonatal apnea, bronchopulmonary dysplasia, neonatal mechanical ventilation, hypotension, increasing mental alertness, enhancing performance, weight loss, T2D, diuretic	Anxiety, jitteriness, restlessness, nervousness, agitation, irritability, delirium, manic behavior, psychosis, panic attacks and increased suicidality
Coca Bolivian Coca, Gu Ko Yi, Inca Health Tea	○ Recreation: source of cocaine – mind-altering effects ○ Medicine: ○ Oral: (Chewed) relief of hunger/fatigue, enhancing physical performance. (Tea/Extracts) stimulating stomach function, sedation, and asthma, colds, altitude sickness ○ Topical: corneal, nasal, and throat mucosa anesthesia, severe ophthalmologic pain, and local vasoconstriction	Delirium, mood swings, restlessness, irritability and acute paranoid psychosis
Cowhage Cow itch, Velvet Bean	○ Medicine: ○ Oral: PD, anxiety, arthritis, hyperprolactinemia, parasitic infections, pain, fever, to induce vomiting, improve libido, prophylactically as snakebite remedy ○ Topical: counterirritant for pain, RA, myalgias, stimulates cutaneous blood flow in paralytic conditions, and treat scorpion stings	Acute toxic psychosis, agitation, and paranoid delusions

CAM Products	Purported Indication	Potential Effect
Creatine Cr, Creatin, Dicreatine Malate, C, Phosphocreatine, Tricreatine Malate	○ Medicine: improving athletic performance/muscle strength, age related muscle loss, bone mineral density, cerebral creatine deficiency syndromes, CHF, COPD, depression, diabetes, exercise tolerance, fibromyalgia, Huntington's disease, idiopathic inflammatory myopathies, PD, mitochondrial myopathies, MS, muscle atrophy, muscle cramps, neonatal apnea, neurological trauma, Rett syndrome, hereditary motor and sensory neuropathy, schizophrenia, spinal muscular atrophy, and surgical recovery. Also used to slow progression of ALS (Lou Gehrig's disease), osteoarthritis, RA, McArdle disease	Anxiety, irritability, depression, aggression, and nervousness
Ephedra Cao Mahuang, Chinese ephedra, Chinese Joint-Fir, Herbal Ecstasy, Indian Jointfir, Ma Huang, Sea Grape, Teamster's Tea, Yellow Astringent, Yellow Horse	○ Medicine: weight loss/obesity, enhance athletic performance, allergies, allergic rhinitis, nasal congestion, asthma, brochospasm, URTI, colds, flu, fever, chills, headache, nephritis, anhidrosis, joint/bone pain, and edema	Dizziness, restlessness, anxiety, irritability, personality changes, mania and psychosis; a case of suicide attempt reported
Fever Bark Alstonia Bark, Australian Febrifuge, Australian Fever Bush, Australian Quinine, Bitterbark, Devil Tree, Devil's Bit, Dita Bark, Pale Mara	○ Medicine: fever, hypertension, diarrhea, rheumatism, and malaria. It is also used as a stimulant and a uterine stimulant	Irritability and could trigger psychosis
Jimson Weed Angel Tulip, Datura, Devil's Apple, Devil's Trumpet, Jamestown Weed, Locoweed, Mad-Apple, Nightshade, Peru-Apple	○ Recreation: hallucinations and euphoria ○ Medicine: asthma, spastic or convulsive cough, pertussis during bronchitis, influenza, and diseases of the autonomic nervous system	Combative behavior, agitation, severe agitation
Ketogenic diet	○ Recreation: fad diet ○ Medicine: seizures and epilepsy-related diseases ○ Also Known As ○ Classic Long-Chain Triglyceride Ketogenic Diet, Keto Diet, Low Carbohydrate Diet, Low Glycemic Index Treatment, Medium Chain Triglyceride Diet, Modified Atkin's Diet, Very Low Carbohydrate Diet	Unpredictable anger or irritability

CAM Products	Purported Indication	Potential Effect
Khat Abyssinian Tea, Arabian-Tea, Chaat, Chat, Gat, Ghat, Somali Tea, Tchaad	○ Medicine: diabetes, muscle strength, depression, fatigue, obesity, gastric ulcers, headache, male infertility, facilitate labor, suppress need for food/sleep, decrease sexual desires, increase focus, and increase aggression	Aggressiveness, anxiety, and manic behavior
Manganese Manganese and assorted salts, Manganeso, Manganum	○ Medicine: manganese deficiency, osteoporosis, osteoarthritis, microcytic anemia, weight loss, and symptoms of premenstrual syndrome (PMS)	Mood disturbance
Marijuana Blunt, Bud, Cannabis, Dope, Hash, Hashish, Mary Jane, Medical Marijuana, Pot, Weed	○ Recreation: mind-altering effects, hallucinations, euphoria, relaxation ○ Medicine: pain and MS symptoms	Anxiety, paranoid thinking or dissociation
Rauvolfia Vomitoria African Serpentwood, African Snakeroot, Akanta, Poison Devil-pepper, Rauwolfia vomitoria, Serpent Snake Root, Serpent Wood, Swizzle-Stick Tree	○ Medicine: seizures/convulsions, psychosis, fever, weakness, insomnia, intestinal disorders, liver health/jaundice, mental disorders, pain, arthritis, cancer, hypertension, diabetes, sedative, and emetic. ○ Used in workout supplements to increase blood flow, improve mood, and increase fat burning	Anxiety
Scopolia Belladonna, Japanese Belladonna	○ Medicine: spasms of the GI, bile ducts, and urinary tract, liver/gallbladder complaints, diuretic, sedative, hypnotic, narcotic, for dilating pupils, and pain relief	Aggressive and auto-aggressive behavior
Sida cordifolia Country Mallow, Heartleaf, Indian Chikana, Indian Ephedra, White Mallow	○ Medicine: asthma, tuberculosis, common cold, influenza, headaches, nasal congestion, cough, UTIs, oral mucositis, edema, CVD, stroke, Bell's palsy, PD, sciatica, schizophrenia, postherpetic neuralgia, neuropathy, anorexia nervosa, RA, and other rheumatic conditions	Irritability and anxiety
St. John's Wort Amber, Amber Touch-and-Heal, goatweed, hypereikon, Klamath weed, Racecourse weed, SJW, Tipton weed	○ Medicine: depression, dysthymia, heart palpitations, mood disturbances, menopause, somatization disorder, PMS, ADHD, social phobia, OCD, SAD, smoking cessation, fibromyalgia, CFS, burning mouth syndrome, headache, migraine headache, muscle pain, neuralgia, polyneuropathy, sciatica, angioplasty, fatigue, loss of appetite, insomnia, anxiety, cancer, glioma, vitiligo, herpes simplex, HIV/AIDS, PCOS, hepatitis C, weight loss, as a diuretic, and IBS	Anxiety and irritability

AD = Alzheimer's disease; ADHD = attention deficit-hyperactivity disorder; ALS = amyotrophic lateral sclerosis; CFS = chronic fatigue syndrome; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; IBS = irritable bowel syndrome; MS = multiple sclerosis; OCD = obsessive-compulsive disorder; PCOS = polycystic ovary syndrome; PD = Parkinson's disease; PMS = premenstrual syndrome; RA = rheumatoid arthritis; SAD =seasonal affective disorder; SLE = systemic lupus erythematosus; T2D = type 2 diabetes; URTI = upper respiratory tract infections; UTI = urinary tract infection

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