PHARMACY PHACTS

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Neurological Side Effects from Opioids

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Medications that bind to opioid receptors are prescribed in a diverse set of painful conditions. [1] While useful to treat moderate to severe pain, they also induce central nervous system (CNS) adverse effects. [2] These effects are grouped into three general categories: decrease in the level of consciousness, decrease in the rate of cognitive processes and the ability to react, and direct toxic effects of opioids on neurons. These side effects are common with 73-81% of patients experiencing memory deficits, 35-37% experiencing sleep disturbance, and 20-60% experiencing sedation.[3] The incidence of opioid-induced neurotoxicity such as myoclonus can range from 2.7%-87% depending on the opioid and the dose.[4]

Opioids commonly cause sedation and drowsiness on initiation, but tolerance often develops with continued use.[4,5] This sedation may affect a patient's reaction time and ability to communicate. Sleep disturbances have also been caused by opioids, specifically fragmented sleep, REM suppression, and non-REM sleep during both stage 2 and slow wave sleep. These effects may be induced by the pain process given that pain itself can cause sleep abnormalities.

Cognitive impairment may occur and lead to decreased attention span, disorientation, agitation, hallucinations, and delirium. Studies have shown that parenteral opioids carry the highest risk for cognitive impairment, but this may also occur with oral doses in compromised populations. Meperidine has been shown to cause the greatest psychomotor and cognitive impairment; there is less with hydromorphone, and even less with morphine. [6] Studies conclude that opioids cause the greatest cognitive and psychomotor impairment during initiation and dose escalation.[7]

Neurotoxicity is a major adverse effect of opioid analgesia and this may result in symptoms ranging from mild confusion or drowsiness to delirium and seizures.[8] It is more common with opioids that have active metabolites.[8] Opioids have also been known to cause myoclonus and hyperalgesia.

New FDA Warning: Fluoroquinolone-Associated Psychiatric Adverse Events

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The Food and Drug Administration (FDA) continuously monitors the safety profile of FDA-approved medications through examination of post-marketing adverse event reports. Fluoroquinolones, a class of widely-used antibiotics, includes levofloxacin (Levaquin), the one carried here at Sheppard Pratt, as well as moxifloxacin (Avelox), ofloxacin, gemifloxacin (Factive), delafloxacin (Baxdela), and ciprofloxacin (Cipro). This class already carries boxed warnings for increased risk of tendon rupture, worsening symptoms for patients with myasthenia gravis, and the risk of serious irreversible nerve damage.

A comprehensive review of adverse events reported to the FDA and published case reports resulted in a new safety warning addressing psychiatric adverse events in July 2018. Psychiatric events experienced by patients include disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium. In addition, the FDA has changed the requirements for safety labeling in regard to such events to remain "consistent across the labeling of the fluoroquinolones class," whereas previous labeling was individualized to each medication in the class. Due to all the safety concerns, the FDA recommends that the use of these antibiotics be reserved for patients who do not have appropriate alternative treatments for bacterial infections.

"Quick-to-Dissolve" Doesn't Always Mean "Fast-Acting"

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What causes a medication to work faster or slower? Many factors come into play: the nature of the drug itself, whether it's a solid or liquid, how it is formulated, and the route of administration, to name just a few. When it comes to addressing acute behavioral issues, especially agitation, we all want a medication to be safe and effective QUICKLY!

A number of pharmacologic options exist for the management of acute agitation in patients not responding to verbal de-escalation or other behavioral interventions. Although some antipsychotics are approved for acute agitation, many agents are utilized "off-label" in this way. Patient willingness to take medications orally avoids the need for an injection, but there are a number of pharmacokinetic and administration factors when choosing an agent.

All oral formulations, whether standard tablets, capsules, or orally-disintegrating tablets (ODTs), require patient cooperation to take the drug properly. It is commonly believed that ODTs provide a more rapid onset of action; however, an orally- disintegrating formulation is NOT absorbed from the mouth where it dissolves, but rather from the stomach, just like tablets that are swallowed. Therefore, ODTs require the same amount of time to reach peak bloodstream concentrations as a standard tablet formulation. However, they often require less patient cooperation and are more difficult to "cheek."

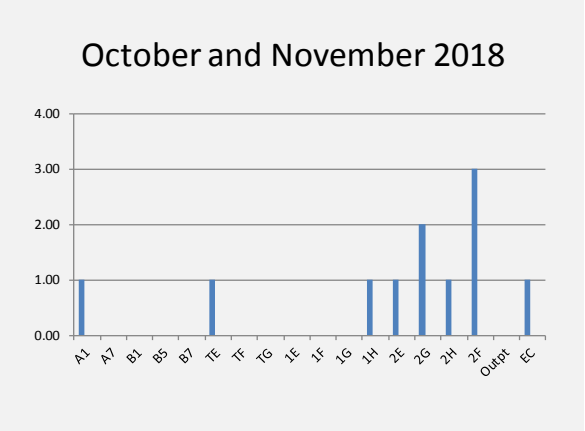
Please see the table below for important pharmacokinetic considerations as well as additional factors surrounding the use of selected antipsychotics in the management of acute agitation. Please note that the onset of action of all these products is much shorter than the "time to peak concentration" listed.

Pharmacokinetic Parameters of Select Oral Antipsychotic Formulations			
Medication	*Available Dosage Form*	*Time to Peak Concentration*[#]	*Additional Considerations*
Haloperidol	Standard tablet	2-6 hours	
Quetiapine	Standard tablet	Children and Adolescents 12 to 17 years: 0.5-3 hours Adults: 1.5 hours	
Chlorpromazine	Standard tablet	30-60 minutes	
Aripiprazole	Standard tablet	3-5 hours	High fat meals delay the peak of parent drug by 3 hours and the peak of dehydro-aripiprazole (active metabolite) by 12 hours.
Olanzapine	Standard tablet	5-6 hours	Maximum plasma concentrations following IM administration are 5 times higher than maximum plasma concentrations produced by an oral dose.
	Orally disintegrating tablet (ODT)	5-6 hours	
Risperidone	Standard tablet	3 hours	
	Orally disintegrating tablet (ODT)	3 hours	
Asenapine	Sublingual tablet	0.5-1.5 hours	Allow to completely dissolve under the tongue. **Do not split, crush, chew, or swallow.** Avoid eating or drinking for at least 10 minutes after administration.

[#]Caution with repeated dosing prior to time of peak concentration due to accumulation and potential for delayed onset of adverse effects

Adverse Drug Reactions (ADRs)

Number of ADRs reported



You may report an ADR by calling x3784 or entering the data into the Sunrise Allergies System.

Formulary changes

- Mirabegron (Myrbetriq), a beta-3 agonist indicated for the treatment of overactive bladder, was added to the formulary (25 mg tablet).

Drug shortages

- Epi pen 0.3 mg: ongoing nationwide shortage. Some in stock with intermittent availability. Can give IM Epi if run into crisis.
- Diphenhydramine injection: supply adequate at present time ($1.25/vial). May use hydroxyzine (Vistaril) injection as alternative (price has doubled to $10/vial).
- Haloperidol: 0.5mg, 1mg, 2mg tablets unavailable; 5mg and 10mg tablets on short supply.
- Diltiazem SR 90 mg: resolved
- Stelazine: all strengths unavailable. Limited supply will soon expire.
- Labetalol injection (ECT): on backorder with no release date

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All references are available upon request.