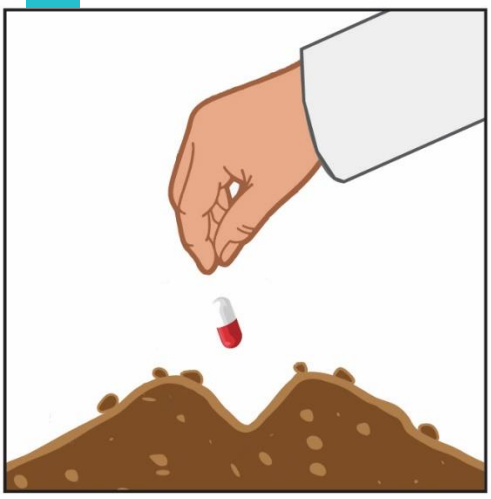
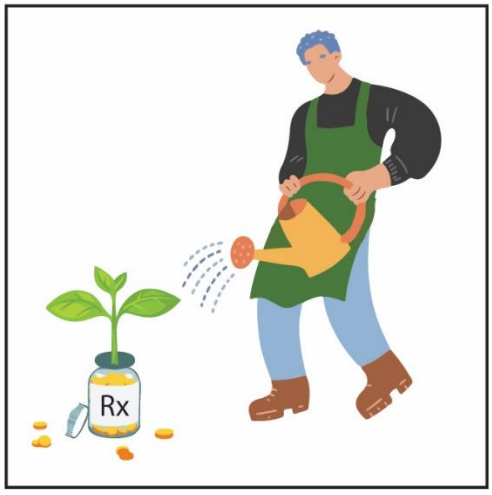
The Pharm-ER's Almanac

April 1st, 2021

Volume 1, Issue 1





In this Issue:

Editor's Welcome

Welcome to the inaugural issue of the Pharm-ER's Almanac. The goal of this publication is to discuss all things drug that might pertain to the ED clinician. As you all know, the ED is a place where you can witness the magic that happens when a top-notch multidisciplinary team goes to work, and medicines are intertwined among that.

We use drugs to treat and cure diseases, alleviate symptoms, and even make or confirm diagnoses. It's a rare patient who darkens the door of the ED and doesn't wind up getting something (I'm not sure you can even say the words "abdominal pain" without being given ketorolac and hyoscine). We have drugs to make you sleep and drugs to wake you up, drugs to make you pee and drugs to make you stop peeing. We even have drugs that change the colour of your pee, if that's your thing. There isn't a whole lot drugs can't do.

On the flip side, we spend a great deal of time treating the unwanted effects of drugs. Patients take drugs, both prescribed and otherwise, that land them at our doorstep. Luckily for us we're armed with just the thing to counteract these adverse effects: more drugs!

To illustrate the dichotomy of drugs, you need look no further than the two epidemics currently sweeping through our continent: opioids and COVID-19. Drugs fuel one, while offering hope toward the end of the other. This newsletter hopes to explore this dichotomy, and help us make sense of some of the issues we face as ED clinicians on a daily basis.

That being said, this newsletter is designed to be for everyone in the ED, and in time, by everyone. I hope to enlist the help of the diverse group of professionals (and equally diverse opinions) found in the ED. If you have something to say about drugs in the ED, the Pharm-ER's Almanac wants to hear from you! Guest writers from all backgrounds will help make this a success, so reach out if you're interested.

If you like something you see, let me know. If you don't like something, let me know. Do you disagree with something presented and want to showcase a different viewpoint? You guessed it, let me know. Feedback from you, the reader (hopefully plural, but I won't get ahead of myself) will help ensure the newsletter publishes relevant content.

Liam

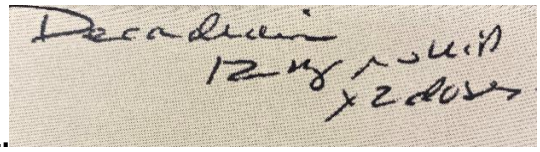
Special Thanks (In no particular order)

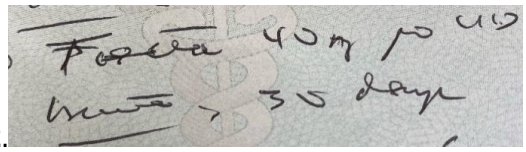
Sarah Mulrooney and Melissa Yuzda – Guest Authors
Leslie Manual and Jonathan Stevens – Content Reviewers
Jennifer Shea – Laboratory Data
Mandy Peach – SJRH EM Website Editor
Sarah Saunders – Phun Zone Contributor
Heather Woods – Cover Comic
SJRH ED Staff – For everything that you do!

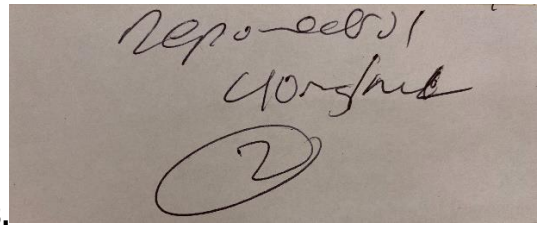
Questions? Comments? Scathing reviews? Interested in writing a guest article or letter to the editor?

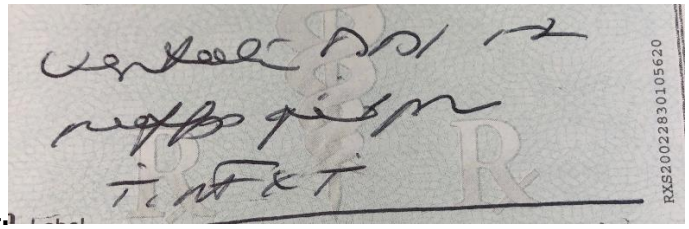
Phun Zone!

Before getting into the serious content, start with something light! Pharmacists put their handwriting interpretation skills to the test every day, now it's your turn. Take a look at the 4 images below and see if you can interpret the prescription. Email guesses to liam.walsh@horizonnb.ca – the first with all 4 correct will get a shout out in the next issue.

1. 

2. 

3. 

4. 

To (Collect) Pee or Not to (Collect) Pee, That is the Question

Take a moment to think back on the last 10 overdose patients you've seen. How many of these patients were ordered a Urine Abuse Screen (UAS)? Probably most. Now think about the number of times that UAS result changed the course of care you provided. Were antidotes given, ET tubes placed, or disposition decided based on the results? Probably not.

The UAS, as it is available to SJ ED clinicians, is an antibody-based test that determines the presence of a panel of drugs/metabolites at concentrations above a pre-determined cutoff. While a potentially useful screening tool in some situations, its many pitfalls limit its usefulness in the ED setting. False positive and negative results abound. Qualitative assays are unable to correlate with clinical toxicity. Most importantly, however, the results don't seem to alter the management of ED patients.

When looking at UAS (and most laboratory test) results, we often take the results at face value. We must stop and consider, however, the limitations of the test itself. As the below table will illustrate, both false positives and negatives can cloud the picture painted by the UAS. Not all benzodiazepines, for example, are detected at the same rate, so a false negative may occur for a patient taking a poorly reactive benzodiazepine. Fentanyl as well, is not detected by the opioid screen, which may provide false reassurance to a clinician looking at a negative opioid result.

The assay with the highest potential for false positive results is the amphetamine. Therapeutically used medications such as diphenhydramine and ranitidine can trigger a positive amphetamine screen, leading possibly to unwarranted further testing or suspicion of drug abuse. (See Table 1 on page 4).

The Urine Abuse screen is a qualitative assay, meaning the test tells you if the drug in question (errors outlined above aside) is there or not. There is no quantitative component, so it's impossible to tell from the test if the drug is present in therapeutic levels, toxic levels or somewhere in between. This presents 2 conundrums to the ED clinician. First, patients often overdose on medications they're prescribed therapeutically, in which case the UAS is likely positive for that drug anyway.

Second, drugs can remain in a patient's urine at detectable levels for days-months after ingestion. This makes the UAS more of a snapshot of drugs used in the past, rather than anything correlated with acute toxicity (history and physical exam is infinitely more useful). On top of this, as I'm sure you've experienced, urine samples aren't always free flowing (pun intended), so it may be hours before you even have the urine to test. This is far too late to be useful in clinically managing a more severe toxicity.

While urine screens do provide the clinician with more information, this information has been shown to not affect management of patients. A systematic review from the journal *Clinical Toxicology*, including adults and children, across a wide variety of presentations (psychiatric, trauma, medical) concluded that the results of a Urine Drug screen (synonymous with our UAS) did not alter the management of these ED patients.[1] Furthermore, it negatively impacted ED length of stay in another study.[2]

According to data pulled from 2021 SJRH ED visits so far, approximately 140 urine abuse screens per month are ordered. If this average is consistent, the ED will spend a roughly estimated $48,000 per year on urine abuse screens. While this isn't a bank-breaking sum compared to some other hospital expenditures, the value-for-dollar ratio isn't terrific.

For your next 10 overdose patients I ask that you pause for a moment and ask yourself "will anything on this test affect how I treat my patient?" If that answer is no, and the evidence suggests it probably is, consider saving the lab dollars for higher-yield investigations.

By Liam Walsh, B.Sc. (Pharm), RPh
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References:

1) Tenenbein M. Do you really need that emergency drug screen?. Clin Toxicol (Phila). 2009;47(4):286-291. doi:10.1080/15563650902907798
2) Riccoboni ST, Darracq MA. Does the U Stand for Useless? The Urine Drug Screen and Emergency Department Psychiatric Patients. J Emerg Med. 2018;54(4):500-506. doi:10.1016/j.jemermed.2017.12.054

Table 1: Technical Data for Urine Abuse Screen (SJRH)

Drug or Drug Class	Threshold for Detection	Calibrator	Approximate Detection Time	Notes/Interpretation
Amphetamines	1000 ng/mL	*d*-methamphetamine	48 hours	The current test measures amphetamine, methamphetamine and the designer amphetamines (MDA, MDMA, MDEA etc). Common drugs that MAY interfere (depending on concentration) include trazodone, labetalol, pseudoephedrine, ranitidine, diphenhydramine, venlafaxine, and bupropion.
Benzodiazepines	200 ng/mL	Nordiazepam	12 hours to 12 days (Excretion times vary widely depending on the drug consumed)	Diazepam + metabolites: up to ~12 days Alprazolam + metabolites: 2-3 days Excretion times vary with other benzodiazepines. **Not all benzodiazepines are detected equally**. Assay is calibrated with nordiazepam so will detect anything that is either metabolized to nordiazepam or has structural similarity to nordiazepam. Cross reactivity of other benzodiazepines ranges from 50- 100%.
Cocaine Metabolite (Benzoylecgonine)	300 ng/mL	Benzoylecgonine	48 - 72 hours	Assay is specific to BEG. Very little cross reactivity to anything else therefore false positive rate is very low.
Cannabinoids	50 ng/mL	Delta-9 Carboxy THC	72 hours (single use) 14-18 days (daily use) >20 days (chronic THC use)	Excretion times vary widely with individual characteristics, dose, acute vs. chronic use, body mass, etc. Also may be possible to obtain a positive result after passive inhalation in a poorly ventilated area.
Opiates	300 ng/mL	Morphine	48 hours	The test used in house is designed to measure codeine, morphine, and to a lesser extent, hydrocodone and hydromorphone (the latter two at high doses only). Hydromorphone and hydrocodone may not be detected at low doses. **Oxycodone, methadone, meperidine (Demerol), and fentanyl do not demonstrate any cross reactivity with the opiates assay**.
Oxycodone	300 ng/mL	Oxycodone	48 hours	This assay is specific for oxycodone only.
Methadone Metabolite (EDDP)	100 ng/mL	EDDP	48 - 72 hours	Specific test for the methadone metabolite, EDDP.
Fentanyl	2 ng/mL	Fentanyl	24 - 72 hours	Assay is specific to fentanyl with little cross - reactivity to norfentayl (a shared metabolite with other fentanyl analogues). Therefore, will likely not detect fentanyl analogues although this hasn't been extensively tested by us or the manufacturer.

*The preceding table is accurate as of March 18, 2021 and applies to immunoassay screening done in house at SJRH only. Drug concentrations are not normalized to creatinine prior to determining if a drug is absent or present, therefore extremely dilute urines may result in false negatives. Also, please note that detection times are an estimate only as this depends on a number of factors including the patient's hydration status, dose/amount taken, metabolism, urine pH, etc. Table courtesy of Dr. Jennifer Shea, PhD – Clinical Biochemist, SJRH.

Key Points on Immune Checkpoint Inhibitors from an Oncology Pharmacist

Overview:

- Immune Checkpoint Inhibitors (ICIs) encompasses anti-PD-1/PDL-1 therapies (such as pembrolizumab, nivolumab, atezolizumab, durvalumab and avelumab), as well as anti-CTLA-4 therapies (such as ipilimumab).
- ICIs may be used as monotherapy, in combination (ipilimumab + anti-PD-11/PDL-1), or in combination with traditional chemotherapy.
- BC Cancer currently has standardized protocols for the use of ICIs in the setting of genitourinary Ca, head and neck Ca, lung Ca, lymphoma, melanoma and Merkel cell carcinoma. The applicability of these agents continues to expand.

Mechanism of Action:

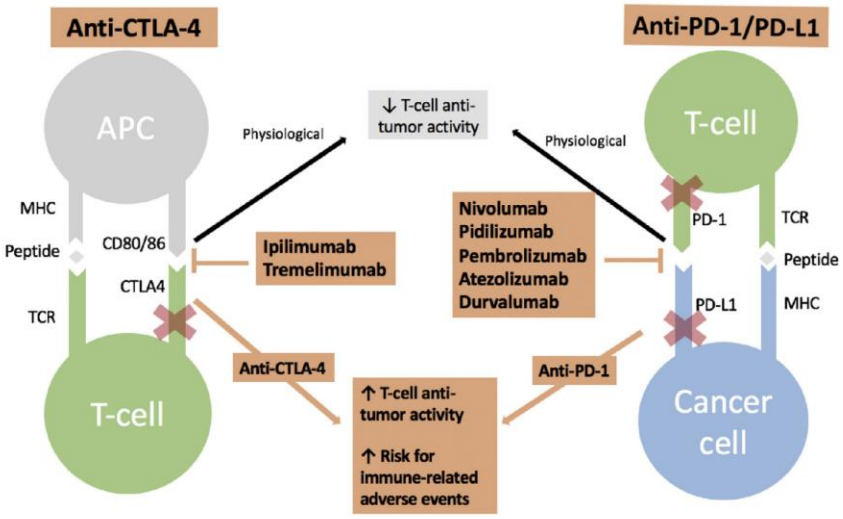


Figure 1. Mechanism of action of both anti-CTLA-4 and anti-PD-1 agents. An APC presents a foreign or perceived non-self-peptide fragment via its MHC, which binds and stimulates a TCR. Activation of the TCR leads to expression of CTLA-4, which binds with a greater affinity to CD80/86 and promotes self-tolerance and prevents autoimmunity in normal conditions. The anti-CTLA-4 therapies (i.e., ipilimumab and tremelimumab) inhibit this co-inhibitory pathway and lead to enhanced T-cell stimulation and tumor surveillance. On the right side of the figure, a similar mechanism is seen for the anti-PD-1/PD-L1 agents. PD-L1 is expressed on cancer cells (among others) and also inhibits T-cell activation when binding to the PD-1 expressed on the surface of the T cell. Anti-PD-1/PD-L1 treatment leads to the inhibition of this inhibitory pathway and leads to enhanced T-cell activity against tumors. However, both of these pathways come at the cost of immune-related adverse events. APC = antigen presenting cell; CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4; PD-1 = programmed death-1; PD-1L = programmed death-1 ligand; MHC = major histocompatibility complex; TCR = T-cell receptor.

Hryniewicki, A. T., Wang, C., Shatsky, R. A., & Coyne, C. J. (2018). Management of Immune Checkpoint Inhibitor Toxicities: A Review and Clinical Guideline for Emergency Physicians. The Journal of Emergency Medicine, 55(4), 489–502. https://doi.org/10.1016/j.jemermed.2018.07.005

The immune system naturally uses CTLA-4 and PD-1/PD-L1 to downregulate the activity of T cells allowing for tolerance and preventing damage from immune system activation. Some malignant cells will hijack this, which prevents the immune system from recognizing them as a problem. Immunotherapy interacts with receptors on either T cells, or the cancer cells themselves. In doing so, the immune system is no longer "fooled" by the malignant cells' misuse of this regulation system. The immune system is then better able to recognize malignant cells and mount a response against them.

Where Things Can Go Awry: Inhibition of these natural downregulation systems can result in loss of tolerance, resulting in broad immune-related attacks to <u>any</u> organ system. These are known as immune-related adverse effects- irAEs.

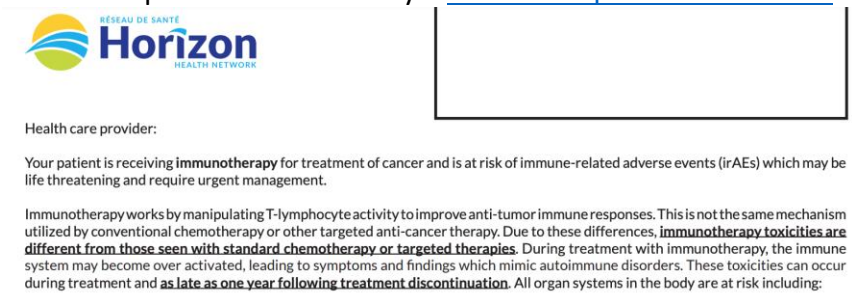
Most Commonly Affected Organ Systems:

- Dermatologic (Beginning 2-3 weeks into treatment)
- Gastrointestinal/Hepatic (Beginning 6-7 weeks into treatment)
- Endocrine (Beginning 9 weeks into treatment)
- Pulmonary (Beginning 7-24 months into treatment)

*<u>Note: **These timelines are estimates only**. ANY ORGAN SYSTEM CAN BE AFFECTED AT ANY TIME. irAEs can spontaneously occur up to two years from the last dose of ICI.</u>* irAEs relating to ipilimumab may appear sooner than with other ICIs.

How to Know if Oncology Patients are Receiving ICIs:

1) Most HHN patients should carry a healthcare professional letter such as this:



Health care provider:

Your patient is receiving **immunotherapy** for treatment of cancer and is at risk of immune-related adverse events (irAEs) which may be life threatening and require urgent management.

Immunotherapy works by manipulating T-lymphocyte activity to improve anti-tumor immune responses. This is not the same mechanism utilized by conventional chemotherapy or other targeted anti-cancer therapy. Due to these differences, **immunotherapy toxicities are different from those seen with standard chemotherapy or targeted therapies**. During treatment with immunotherapy, the immune system may become over activated, leading to symptoms and findings which mimic autoimmune disorders. These toxicities can occur during treatment and **as late as one year following treatment discontinuation**. All organ systems in the body are at risk including:

2) Can always review in AllScripts by selecting "All Available Charts" in the orders tab, and filter back through the past year's chemo orders, keeping a special eye out for these drugs. However, this is only effective if the patient is treated by an oncologist based in Saint John.

What to Do if irAEs are suspected:

1) Use a grading tool:
   BCCA (more point of care): http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf
   ASCO (more detailed): https://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385
2) If indicated start steroids:
   Prednisone 1-2 mg/kg/day PO
   Corticosteroid eye drops for ocular toxicities
   Consider methylprednisolone 1-2 mg/kg/day IV for some grade 3-4 toxicities or unable to tolerate PO prednisone
3) Notify prescriber/oncologist that an irAE is suspected
4) Consider referral to specialist as applicable (i.e. dermatology, gastroenterology, endocrinology, respirology, etc.)
5) There may sometimes be a role for infliximab. However, this is generally only applicable in grade 3-4 irAEs, after steroids have failed.

By Sarah Mulrooney, BSc (Pharm), ACPR, RPh
Pharmacist – Oncology, SJRH

Additional Reading/References:

Cancer Care Ontario. (2018, March). *Cancer Care Ontario- Immune Checkpoint Inhibitor Toxicity Management Clinical Practice Guideline*. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/52976

Hryniewicki, A. T., Wang, C., Shatsky, R. A., & Coyne, C. J. (2018). Management of Immune Checkpoint Inhibitor Toxicities: A Review and Clinical Guideline for Emergency Physicians. *The Journal of Emergency Medicine*, *55*(4), 489–502. https://doi.org/10.1016/j.jemermed.2018.07.005

Colonel Mustard in the Parlour with a Lead Pipe (Rigidity): A Clue to His Diagnosis?

Antidepressant and antipsychotic use are on the rise in part due to these agents being prescribed for off-label indications and increases in augmentation and combination strategies for psychiatric illnesses. Although seen infrequently, these syndromes can be fatal. Their similar presentations warrant a good understanding of how to differentiate between the two by emergency room clinicians in order to provide prompt and effective treatment. Consider the table below for a guide to differentiation.

	Serotonin Syndrome	Neuroleptic Malignant Syndrome
ONSET	Within 24 hours of increasing the dose or adding a serotonergic agent	Can occur at any point during treatment with an antipsychotic (AP). Majority of cases reported within the first 2 weeks of therapy
***SIGNS/SYMPTOMS**	**TRIAD** (**Neuromuscular, autonomic & mental status changes**) **Mild**: tremors, incoordination, restlessness, headaches, insomnia, nausea, diarrhea, clonus of lower extremities **Moderate**: Hyperreflexia, clonus progression, myoclonus, ocular clonus, shivering/teeth chattering, agitation, diaphoresis, tachycardia, dyspnea, dilated pupils **Severe**: Hyperthermia, hyper/hypotension, sustained clonus or rigidity, confusion, delirium, tonic-clonic seizures, respiratory depression, rhabdomyolysis	**TETRAD** (**Hyperthermia, muscle rigidity, altered mental status, autonomic instability)** Woodbury Stage 1: rigidity &/or tremor Stage II: rigidity, altered mental status, mutism Stage III: mild rigidity, catatonia or confusion, temperature < 38 ^{o}C, HR < 100 bpm Stage IV: moderate rigidity, catatonia or confusion, temperature 38-40^{o}C, HR 100-120 bpm Stage V: severe rigidity, catatonia or confusion, temperature > 40^{o}C, HR > 120 bpm. Symptoms can progress to rhabdomyolysis & AKI
HALLMARK FEATURES	Hyperreflexia, clonus & tremor	Hyperthermia, bradykinesia & severe rigidity (“lead-pipe or cogwheel “)
LABORATORY MARKERS	None	**Increased CK, LFTs & WBC Reduced serum iron Metabolic acidosis in up to 75% of cases
DIAGNOSIS	***Hunter Criteria Medication history Clinical presentation	Medication history Clinical presentation Increased CK
SEVERITY	Can be life-threatening	Can be life-threatening
MECHANISM OF ACTION	Increase in serotonergic activity in the CNS	Not well understood. Theorized to be the result of excessive dopamine blockade (in particular D2) & possibly an extension of extrapyramidal side effects seen with antipsychotics
CAUSATIVE AGENTS	**SSRIs** SNRIs- **venlafaxine** **MAO-Is** **** TCAs (clomipramine & imipramine) Opioids (tramadol, meperidine, methadone, fentanyl) Dextromethorphan St. John’s wort, diet pills L-tryptophan Chlorpheniramine, brompheniramine Illicit drugs: MDMA, amphetamine (not methylphenidate), cocaine Commonly listed but low risk medications include triptans, amitriptyline, cyclobenzaprine, bupropion, mirtazapine, trazodone, ondansetron, metoclopramide, buspirone and lithium	Any **antipsychotic** at any dose, given via any route at any point in therapy. Metoclopramide, domperidone, prochlorperazine & promethazine Abrupt withdrawal of dopamine agonist therapy such as levodopa
RISK FACTORS	Usually the result of a drug interaction involving the combination of serotonergic agents that increase serotonin through different mechanisms. The highest risk being when one of the agents is a MAO-I Serotonergic drug overdose	Rapid AP dose titration, use of higher AP doses Depot AP use, IV AP treatment AP in combination with lithium Prolonged heat exposure Physical restraints Dehydration

	Serotonin Syndrome	Neuroleptic Malignant Syndrome
DIFFERENTIAL DIAGNOSIS	Anticholinergic toxicity, antidepressant discontinuation syndrome, malignant hyperthermia, drug overdose, alcohol/benzodiazepine withdrawal	Anticholinergic toxicity, antidepressant discontinuation syndrome, malignant hyperthermia, drug overdose, alcohol/benzodiazepine withdrawal
TREATMENT/ANTIDOTES	Discontinue offending agent Supportive care Benzodiazepines for agitation, tremor & clonus Cyproheptadine 12 mg po stat then 2 mg q2h or 4-8 mg q4h prn if symptoms persist despite treatment with the above (serotonin antagonist/off-label use)	Discontinue offending agent Supportive care/cooling blankets Dantrolene IV-direct skeletal muscle relaxant for severe rigidity. Initial dose of 1-2.5 mg/kg; repeat dose, if needed, to a maximum cumulative dose of 10 mg/kg. When symptoms are controlled, 1 mg/kg q6h or 1 mg/kg/daily may be used *(Horizon Parenteral Drug manual*) Bromocriptine po (D2 agonist) may be added to dantrolene for severe cases. Benzodiazepines for agitation Antipyretics unlikely to be effective in reducing hyperpyrexia
SYMPTOM RESOLUTION	Within 24 hours	Days to weeks

* Recent literature suggests that these symptoms present on a spectrum and can range from mild to severe involving a combination of neuromuscular, autonomic and mental status changes.

** Laboratory findings are generally nonspecific in patients experiencing NMS and are not seen in all patients. Some patients may present with the list of laboratory results included however an elevation in CK appears to be the most consistent finding.

***Hunter criteria (Need 3 to Diagnose)

1. Spontaneous clonus
2. Inducible clonus AND agitation OR diaphoresis
3. Ocular clonus AND agitation OR diaphoresis
4. Tremor AND hyperreflexia
5. Hypertonic AND temperature > 100.4 ^{o}F AND ocular clonus OR inducible clonus

**** MAO-Is (monoamine oxidase inhibitors) inhibit the metabolism of serotonin, norepinephrine and dopamine and are classified as below.

Nonselective & irreversible: Isoniazid, phenelzine, tranylcypromine.

Nonselective & reversible: Linezolid

Selective & irreversible: Selegiline, rasagiline

Selective & reversible: Moclobemide & methylene blue

By Melissa Yuzda, B.Sc. (Pharm), RPh

Pharmacist – Mental Health, Emergency Department, SJRH

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1. Pileggi DJ et al. Neuroleptic Malignant Syndrome: Focus on Treatment and Rechallenge. Annals of Pharmacotherapy. 2016; 50 (11): 973-981.
2. Foong A et al. Demystifying serotonin syndrome (or serotonin toxicity). Canadian Family Physician. 2018; 64: 720-727.
3. Talton CW. Serotonin Syndrome/Serotonin Toxicity. Federal Practitioner. 2020; 37 (10): 452-459.doi: 10.12788/fp.0042
4. Wijdicks E. Neuroleptic Malignant Syndrome. Wilterdink J, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (Accessed on March 22, 2021)
5. Boyer EW. Serotonin Syndrome (serotonin toxicity). Grayzel J, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com (Accessed on March 22, 2021)

Antidote spotlight: Physostigmine

Consider the following scenario: an 18 year-old female presents to the ED after her parents discovered an empty box of OTC diphenhydramine sleep aid tablets in her bedroom. Upon examination, she is "mad as a hatter", "red as a beet", and all the other components of that mnemonic that I can never remember. She has, by history and symptoms, an anticholinergic toxidrome. You break out the lorazepam, eventually giving so much that she settles into a sort of "sedate delirium", spending the next 24 hours in the ED before finally becoming alert enough to be evaluated by the psychiatry service.

What if there was a better way? Well, there might be: Physostigmine.

Physostigmine is an acetylcholinesterase inhibitor, which prevents breakdown of acetylcholine at the nerve terminal, leaving more acetylcholine available to compete with anticholinergic drugs. This directly reduces the anticholinergic effect of medications. Physostigmine is unique in its class (including neostigmine) in that it crosses the blood-brain barrier and thus has the potential to increase acetylcholine centrally as well, which accounts for its effect on CNS symptoms.

Physostigmine was all the rage in the 1970s, being used even as part of the standard "coma cocktail" along with oxygen, naloxone, dextrose and thiamine.[1] With the progression of the 70s into the 80s, another treatment became popular: the tricyclic antidepressant (TCA). As we now know, TCAs have a wide range of toxicity, including cardiac dysrhythmias, seizures, and anticholinergic delirium.

The anticholinergic delirium of TCAs was a common target for the use of physostigmine until a case series was published in 1980 by Pentel and Peterson outlining two cases of cardiac arrest following physostigmine administration.[2] Following this publication, for various reasons, the fear surrounding physostigmine increased, use plummeted, and benzodiazepines became out mainstay of treatment for the agitated delirium associated with anticholinergic overdose (and pretty much everything else, for that matter).

While these cases are alarming, they may not be generalizable to all anticholinergic toxidromes. The cases were associated with very large TCA ingestions (2.3g amitriptyline and 5g of imipramine), which would be likely to cause cardiac arrest irrespective of physostigmine administration. There was also either no or unknown amounts of bicarbonate given to the patients prior to arrest, which is now the mainstay treatment of the sodium channel blockage associated with TCAs.

Fast forward about 30 years to the 2010s, and interest in the use of physostigmine is again increasing. New evidence is coming to light that may suggest physostigmine use is safer than previously thought. A prospective analysis by Boley Et. Al.[3] reviewed 154 patients with anticholinergic toxicity and found:

- Physostigmine was recommended by Poison Control in 87% of cases, but was used in only 37%.
- 79% of patients who received physostigmine experienced delirium control, vs. 36% of patients who didn't.
- Adverse effects were rare, and occurred equally in both groups.

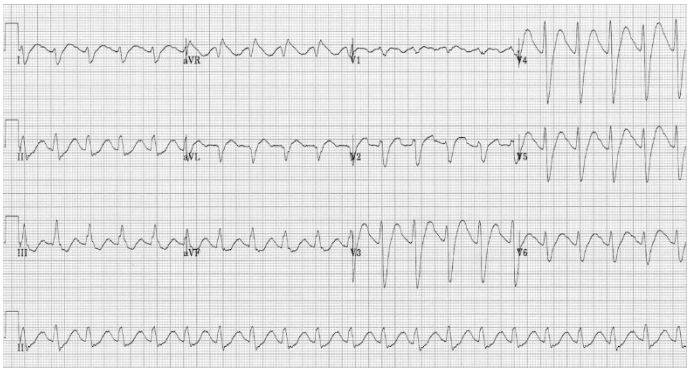
Other studies have found physostigmine to be associated with less ICU admission and less intubation when used to treat anticholinergic toxicity[4,5], although this association has not been consistent across all studies.

So physostigmine is effective for the treatment of delirium associated with anticholinergic toxicity, but is it safe? A systematic review by Arens and Kearney identified 2,299 patients who received physostigmine, and concludes it is.[6] Of these, 18% experienced an adverse effect, but a majority of these were mild and self-limiting. Of note, patients given physostigmine who did not have

anticholinergic overdoses suffered adverse events more often than those who did (20.6% vs. 7.7%).

There are patients, however, where physostigmine might not be an ideal treatment. While possibly safe, the evidence may not yet be robust enough to routinely support its use in anticholinergic toxicity associated with TCA overdose. It's probably best to avoid in those patients, especially those with signs of sodium channel blockade (QRS duration >100ms, terminal r wave in aVR – See Figure 1). There are also some standard contraindications that should be observed, including salicylate allergy (depending on the preparation), intestinal or genitourinary obstruction, heart block, bradycardia, and severe asthma. Consultation with a toxicologist is always a great idea if you're unsure.

Figure 1: 12 Lead ECG showing sodium channel blockade



If your ECG looks like this, consider foregoing the physostigmine!

Once you've decided to use it, consider a dose of 0.5-1mg IV over 10 minutes to start, with repeat dosing up to 2mg if partial response is seen. Consider having some atropine at the bedside for the rare event of excess cholinergic effects (hypersalivation, vomiting, diaphoresis).

In NB, physostigmine is stocked in all EDs in the province as part of the provincial antidotes program. It is a medication obtained from outside Canada as part of the Special Access Program, so don't forget to fill out the associated paperwork and remit to pharmacy.

To make a long story short, consider the following:

- Physostigmine is safe and effective for the treatment of anticholinergic toxicity (Limited data for use with TCAs).
- Physostigmine may reduce the risk of patients needing intubation or ICU.
- Physostigmine may reduce the need for benzodiazepines.
- Consider a dose of 0.5-1mg over 10 minutes to start, up to 2mg if needed (consult IWK Poison Control Antidote Manual for full dosing suggestions)

Together, we can end the Physostigma!

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