

Pharmacy Informer

Children's and Women's Health Centre of BC, Department of Pharmacy

Fall 2015

Updates from C&W Pharmacy, Therapeutics and Nutrition (PT&N) Committee

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The C&W PT&N Committee serves as the Pediatric subcommittee to the Provincial Pharmacy and Therapeutics Committee. We continue to have representation from other Health Authorities, in addition to our membership from C&W.

1. Policies & Procedures

The C&W PTN has been busy updating and renewing its medication policies. The following new or updated policies & procedures were approved and are posted on the C&W intranet:

Addition of Drug to Blood/Blood Products

has been updated to allow calcium gluconate addition to albumin for plasma exchange.

Special Access Programme (SAP) Policy

This policy has been updated to include current procedures for accessing SAP medications at C&W via Health Canada.

Dispensing Medications to Caregivers in Distress

is a new policy that was approved to allow physicians at BCCH to provide a limited number of medications to a patient's caregiver in exceptional circumstances.

Epinephrine and Procainamide Drug Infusion Test Protocol

was approved to allow patients to undergo testing for latent heart disease and Brugada syndrome in the Medical Day Unit.

2. Formulary Changes:

Dexmedetomidine was approved for use via the intranasal route in critical care areas. Dexmedetomidine must be given 15 to 45 minutes prior to the procedure, as onset of action is slow relative to other intranasal sedation and analgesia. The Drug Dosing Guidelines were updated to include this route.

3. Medication Backorders:

We continue to be facing shortages of medications and the Pharmacy Department continues to monitor supplies and usage. We appreciate all the assistance in reviewing options to mitigate the shortages (using oral/rectal routes, changing to alternative medications, changing to other brands and strengths, etc).

Clindamycin oral suspension is currently on backorder and very limited supply is available. Doses may be rounded to the nearest capsule size and mixed with water for administration via feeding tube or with applesauce, chocolate sauce or pudding, or other sweet vehicle for oral administration.

Diazepam Emulsion (Diazemuls) has been discontinued by Pfizer, the only manufacturer in Canada. This formulation was rarely used at C&W. Diazepam 5 mg/mL injection remains be available in a propylene glycol base and is an appropriate substitute.

Prochlorperazine (Stemetil) 5 mg/mL injection has been discontinued by Sandoz, the only manufacturer in Canada. Prochlorperazine was indicated for prevention and control of nausea and vomiting due to various etiologies and for the treatment of migraine. Alternate medications for prophylaxis and treatment of nausea and vomiting are: ondansetron, metoclopramide, dimenhydrinate, dexamethasone, methotrimeprazine.

4. Pre-printed Orders:

The following C&W pre-printed orders have been approved since July:

Cardiology Cardiac Catheterization Post Procedure (Daycare)

Diabetic Ketoacidosis (DKA) Inpatient and Outpatient

Fever and Neutropenia – Stable Patient

Fever and Neutropenia – Unstable Patient

PICU Bowel Protocol

Rheumatology Abatacept Administration

Rheumatology Infliximab Infusion

Rheumatology Tocilizumab Administration

WH IVIG Infusion

WH OB Gestational Hypertension and Proteinuria

Antepartum

WH OB Gestational Hypertension and Proteinuria

Antepartum Postpartum

WH NICU Gastroschisis Admission Initial Management

WH NICU Gastroschisis Admission Post Closure Management

The screenshot shows the intranet homepage with a navigation bar at the top. The 'ORDER SETS' menu item is highlighted with a red arrow. Below the navigation bar, there are several sections including 'PHSA NEWS', 'ANNOUNCEMENTS', and 'RESOURCES'. The 'ANNOUNCEMENTS' section features a 'Code Blue Update for the Oak St. Campus' and a '1 saves 8 Be a hero' button. The 'RESOURCES' section lists various tools and services like 'Baby-Friendly Calendars', 'Code of Conduct', and 'Drug Compendium'.

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BC Children's Hospital Fever & Neutropenia Guidelines 2015 Update

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With the publication of the new 2012 international consensus guidelines[1] on the management of fever and neutropenia (FN) in children, our BCCH Oncology/Hematology/BMT team collaborated with Antimicrobial Stewardship to update local guidelines and protocols. Since September 2015, new [stable patient](#) and [unstable patient](#) order sets and algorithms are in use. The major therapeutic updates are:

- **Peripheral blood cultures**, in addition to central line blood cultures, will be drawn upon initial presentation of FN. Best available pediatric literature indicates that ~13% of true bacteremia in febrile neutropenic pediatric patients are detected only by peripheral cultures (i.e. with negative central line cultures).[2,3]
- **Risk stratification**: Patients will be risk stratified using a strategy specifically adapted for BCCH, which will subsequently guide empiric antibiotic regimen selection. Risk assessment includes patient-specific factors (e.g. malignancy type, disease status), treatment-specific factors, and clinical presentation factors.
- **Oral antibiotics for low-risk fever and neutropenia** are recommended if the child is able to reliably tolerate oral intake. Appropriate oral antibiotics have been compared against parenteral antibiotics for FN in both inpatient and outpatient settings in all FN risk groups including pediatric subgroups, and have been shown to be as effective and safe as parenteral antibiotics with no differences in treatment failure, overall mortality and adverse effects.[4] The adoption of an oral antibiotic in low-risk FN allows for outpatient management, with resultant increased convenience, quality of life for patients and caregivers, and reduced exposure to institutional pathogens.[5]
- **Low-risk FN patients can be managed as outpatients** if they are able to tolerate oral levofloxacin, and if careful monitoring and follow-up can be ensured. Multiple studies of outpatient management for low-risk pediatric FN have shown no infection-related deaths and no evidence of increased treatment failure rate.[6-8] In the low-risk outpatient setting, meta-analyses comparing PO versus IV antibiotics show no difference in treatment failure, mortality, or antibiotic side effects, although rates of readmission are slightly higher with PO antibiotics.
- **If a hematology/oncology/bone-marrow transplant patient has a fever but is not neutropenic, ceftriaxone should not be given routinely**. Antibiotic therapy is not required for febrile non-neutropenic patients who are otherwise well, unless there is evidence of a focal infection, in which case antibiotics should be tailored for the infection.
- **Empiric antibiotics for stable high-risk patients with acute myeloid leukemia no longer routinely include vancomycin**. Piperacillin-tazobactam monotherapy is empirically recommended for all stable high risk FN patients, regardless of their hematological/oncological diagnosis.
- **Guidelines for antibiotic discontinuation in low- and high-risk patients are provided** to minimize unnecessary antibiotic exposure in patients without an infection. Antibiotics can be discontinued if the patient's blood cultures remain negative at 48 hours, have been afebrile for at least 24 hours, and have evidence of marrow recovery. In the absence of marrow recovery, discontinuation of antibiotics may also be considered for low-risk patients (Continued...)

at 72 hours with negative cultures and afebrile for at least 24 hours, and in persistently neutropenic high-risk patients after an empiric 7 to 14 days course if the patient is clinically well with no focus of infection, and has been afebrile for at least 48 hours.

Spotlight on levofloxacin

Levofloxacin has been added to our armamentarium and approved by PT&N for addition to the pediatric formulary earlier this year.

- Levofloxacin is an ideal alternative for low-risk fever and neutropenia, as it has a broad spectrum of activity against gram-positive and gram-negative bacteria and atypical respiratory pathogens, rapid bactericidal activity, a favorable pharmacokinetic profile, lack of myelosuppression, good tolerability, and has been investigated as empiric therapy for FN patients.[9,10]
- Oral levofloxacin is well-absorbed with a bioavailability of 99%, exhibiting concentration-dependent killing and a long half-life allowing for twice-daily dosing in children less than 5 years old, and once daily dosing for children 5 years and older. Pharmacokinetics and safety have not been systematically studied in children under 6 months of age, and use in that age group is therefore not recommended at this time.
- Although fluoroquinolones have traditionally been avoided in the pediatric population because use in juvenile laboratory canines is associated with formation of cartilage lesions, inflammation and subsequent destruction of weight-bearing joints, retrospective and prospective assessments have found a low incidence of arthropathy and an excellent general safety profile in children.[11] The Levaquin Pediatric Program, initiated in 1998 to assess the efficacy and safety of levofloxacin in children, has found minimal risk of reversible musculoskeletal adverse effects, and there have been no reports of irreversible damage.
- A liquid formulation is not commercially available, but tablets can be crushed, although this yields a bitter taste. An oral suspension can be compounded by our BCCH inpatient and outpatient pharmacy.
- Levofloxacin is not a Pharmacare benefit, and limited community pharmacies will compound levofloxacin suspension. The ambulatory pharmacy in BC Children's Hospital can dispense levofloxacin suspension during its opening hours.

Oncology/Hematology/BMT and Antimicrobial Stewardship will closely monitor the use and outcomes of the new F&N guidelines. An assessment to ensure efficacy and safety is planned for early 2016 prior to expansion to sites outside of BCCH.

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Buprenorphine in Pregnancy and Lactation

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Reviewed by: Stacey Tkachuk, BScPharm, ACPR

Opioid dependence is a chronic, recurrent medical illness associated with increased morbidity and mortality and represents a significant health issue in Canada.[1] Opioid use in pregnancy is not uncommon.[2] Untreated opioid misuse during pregnancy can result in obstetric complications including preeclampsia, antepartum and postpartum hemorrhage, premature labour, spontaneous abortion, and placental abruption. Neonatal complications include growth restriction, low birth weight, neonatal abstinence syndrome (NAS), and neurobehavioral problems.[2-4] Pregnant women with substance abuse disorders are less likely to seek prenatal care and have higher rates of infections including HIV and hepatitis.[2] Opioid substitution treatment is regarded as an effective treatment for opioid dependence and an evidence based harm reduction intervention.[1] For decades, methadone maintenance therapy has been the standard treatment for opioid dependence, including the pregnant population.[2,5] In 2007, Health Canada approved a buprenorphine containing product as an alternative to methadone for substitution treatment of opioid drug dependence.[5]

Buprenorphine is a partial agonist at the μ (mu) opioid receptor with high binding affinity but low intrinsic activity at these receptors.[6] Buprenorphine displaces other opioids from receptors and blocks opioids from further binding.[7] Buprenorphine has a slow dissociation rate from opioid receptors allowing for prolonged receptor blockade and suppression of withdrawal. The effect of withdrawal suppression is dose related.[7] However, unlike full opioid agonists (e.g. methadone, morphine, heroin), buprenorphine has a ceiling effect; past a certain point, further dosage increases do not increase pharmacological effect and classic opioid effects (i.e. sedation, euphoria) plateau.[8] As a result, buprenorphine may have a lower potential for abuse and less risk of respiratory depression.[7]

The oral absorption of buprenorphine is poor due to hepatic first pass metabolism, therefore, is taken by the sublingual route.[6] It is primarily metabolized in the liver via CYP3A4 into an active metabolite, norbuprenorphine, however, it is not known whether this metabolite contributes to the overall effect of buprenorphine.[6,7] Buprenorphine's mean elimination half-life is 37 hours.[6] It is mostly eliminated in the feces (70%) with the remainder eliminated in the urine.[6,9] Buprenorphine should be avoided in patients with severe liver dysfunction. No dosage adjustments are required in renal impairment.[6]

Limited information exists on the pharmacokinetics of buprenorphine in pregnant patients, however, dosage adjustment may be required as pregnancy advances. Lower maximal and 24 hour plasma concentrations and enhanced renal elimination have been demonstrated in pregnancy compared to postpartum in patients taking buprenorphine.[10,11]

The most common side effects of buprenorphine are similar to that of other opioids and include sedation, headache, dizziness, nausea, vomiting and constipation.[6,12] While the risk of respiratory depression with buprenorphine use may be lower compared to full opioid agonists, it is still a risk. Significant respiratory depression causing death has been reported particularly when high doses were administered to opioid naïve individuals or with concomitant administration of buprenorphine with benzodiazepines, alcohol or other depressants.[6] Due to buprenorphine's high binding affinity for the opioid receptor, higher doses of naloxone may be required to reverse respiratory depression.[13] Rare cases of hepatotoxicity associated with buprenorphine use have also been reported and it is suggested to monitor liver function tests at baseline and periodically throughout therapy.[6,12] Clinically significant drug interactions can occur with buprenorphine as it is a substrate of the enzyme CYP3A4. Any medications that inhibit or induce this enzyme may result in increased or decreased buprenorphine plasma concentrations, respectively, and dosage adjustments may be required.[6]

Dosing buprenorphine occurs in two stages, induction and maintenance, and will depend on individual patient characteristics including type of opioid dependence, time since last opioid use and the degree of opioid dependence.[5] Due to buprenorphine's high affinity for opioid receptors and its ability to displace other opioids from binding sites, to avoid precipitating acute withdrawal, initiation of buprenorphine should only commence when there are clear signs of withdrawal.[5] Usual induction doses are 2-4 mg to be reassessed for effectiveness, at which time further doses can be considered up to a maximum of 8 mg on day one. Usually, the total amount required by the patient on day one is prescribed for the following day and then further dosage adjustments are made in 2-4 mg increments based on patient response until an optimal dose is reached.[5]

Compared to placebo, buprenorphine improves treatment retention and reduces illicit opioid use in patients with opioid dependence and is comparable to methadone in terms of efficacy in all populations, including pregnant women.[4,14,15] An often cited advantage of buprenorphine compared to methadone in the maternal population is that it may be associated with less NAS, including lower doses of morphine required to treat NAS, shorter NAS treatment durations, shorter neonatal hospital stays and improved neonatal outcomes including higher mean gestational age, weight, length, and head circumference at birth.[16,17] However, these results are limited by confounding and require further study.

Methadone remains a first line treatment in pregnant women due to a greater accumulation of evidence supporting its efficacy and safety and the lack of long-term data on *in utero* exposure of buprenorphine.[2] However, the available safety data on buprenorphine use during gestation is reassuring and does not seem to be associated with congenital anomalies from animal models and limited human data of use during the first trimester.[18]

The only Health Canada approved form of buprenorphine is Suboxone®. Suboxone® is a fixed combination product of buprenorphine and naloxone in a 4:1 ratio available as sublingual tablets in the following strengths:[6]
Buprenorphine 2 mg/naloxone 0.5 mg **AND** Buprenorphine 8 mg/naloxone 2 mg

This combination product is to deter buprenorphine misuse and diversion. Naloxone, an opioid antagonist, is minimally bioavailable when taken via the oral or sublingual route. However, when administered via the intranasal or parenteral routes, sufficient naloxone is available to render buprenorphine inactive and precipitate acute withdrawal.[6] There is limited data on the use of naloxone during pregnancy, therefore, despite naloxone's minimal systemic bioavailability when given via the sublingual route, it is recommended that pregnant women use single entity buprenorphine products for opioid substitution therapy.[2,3] A single entity buprenorphine product, Subutex®, is available through Health Canada's Special Access Program. To avoid destabilization in women who become pregnant that were already receiving the combination product, therapy can be continued with Suboxone® until the single entity product can be obtained. While limited information on buprenorphine and lactation exists, buprenorphine is considered compatible with breastfeeding.[2,3,15] Buprenorphine is excreted into human milk, however, because of the poor bioavailability when taken orally, the amount of buprenorphine reaching the infant is likely clinically insignificant and no untoward effects on breastfeeding infants have been reported.[19] (...Continued on page 6)

Tricyclic Antidepressant Poisoning and Current Controversies

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Reviewed by: Shan Yin, MD, MPH (Emergency Department Physician and Medical Toxicologist)

The tricyclic antidepressants (TCAs) include amitriptyline, desipramine, doxepin, imipramine and nortriptyline. TCAs are commonly used for the treatment of a variety of conditions including depression, anxiety, neuropathic pain, insomnia and as migraine prophylaxis. In children, the TCAs may also be used to treat nocturnal enuresis and in conditions such as cyclic vomiting syndrome.[1,2] TCA overdose continues to have a high associated mortality rate, with approximately half of all deaths related to antidepressants attributed to TCAs.[1]

Pharmacology

The TCAs are weak bases that act as norepinephrine (NE) and serotonin (5-HT) re-uptake inhibitors, thus increasing the concentrations of NE and 5-HT at CNS receptors. Other pharmacologic effects include competitive muscarinic and alpha-1 antagonism, histaminic antagonism and blockade of cardiac myocardial fast sodium channels.[1,2] As a result of their sodium channel blockade, TCAs are referred to as having "quinidine-like" effects and may be classified as type IA antiarrhythmics.[1] The significant antimuscarinic (anticholinergic) activity of the TCAs has limited their therapeutic use due to concerns related to adverse effects.[1]

Pharmacokinetics

TCAs are highly lipophilic, weak bases and are rapidly absorbed from the gastrointestinal tract. Peak serum concentrations are reached 1 to 3 hours following ingestion.[2] As a result of their lipophilicity, TCAs are quickly distributed into tissues following absorption and have high volumes of distribution as well as long half-lives, ranging from 9-92 hours depending on the drug.[3] As a result of saturable metabolism, the half-life may be prolonged in overdose. Furthermore, TCAs are highly protein-bound (up to 95%), but free (unbound) drug concentrations are increased in acidemia and may potentiate toxicity.

Clinical Effects in Overdose

Following ingestion, symptom onset is usually within 4-6 hours. In massive overdose, symptoms may occur within 1 hour.[4] In overdose, TCAs mainly affect the CNS and cardiovascular systems and produce significant anticholinergic effects. The clinical features in toxicity are a direct extension of the multiple pharmacologic actions as described above (Figure 1).

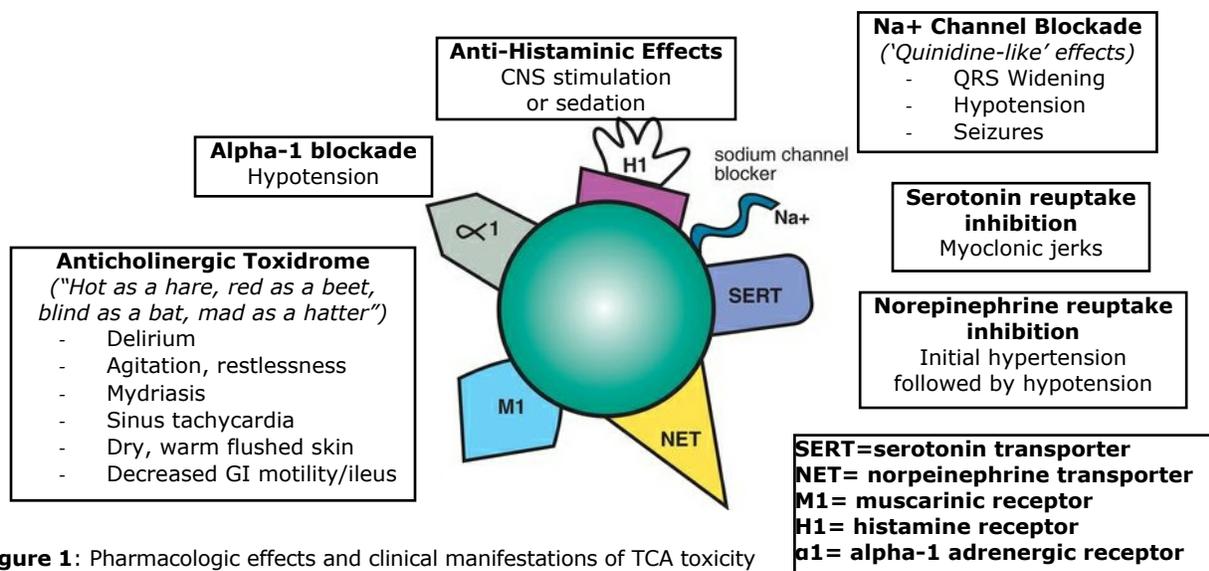


Figure 1: Pharmacologic effects and clinical manifestations of TCA toxicity

There is no specific antidote that reverses all life threatening signs and symptoms of TCA toxicity. The two main adverse effects of TCA overdose are seizures and ventricular dysrhythmias.

Seizures usually occur as an early complication and are unlikely to develop more than 12 hours post ingestion.[2] The majority of seizures are brief and self-terminating. However, even brief seizures can cause broadening of the QRS duration and hypotension through worsening of acidosis. There is no evidence to support the use of prophylactic treatment for patients thought to be at risk of developing seizures. Seizures that are not self-terminating should be treated with benzodiazepines, followed by barbiturates or propofol, if required.[6] Flumazenil should be avoided in suspected TCA overdoses because of numerous case reports of seizure induction with this drug.[4]

In the meta-analysis by Bailey et al.,[7] ECG abnormalities were shown to be good predictors of serious complications (ventricular arrhythmias, seizures and death). A QRS duration of ≥ 100 ms is the strongest arrhythmia predictor (up to 50% incidence of arrhythmias when >160 ms). Sodium bicarbonate is considered first-line treatment for TCA overdose induced arrhythmias regardless of acid-base status. The sodium load provided in a bolus of sodium bicarbonate helps to overcome TCA toxicity due to sodium channel blockade. Furthermore, sodium bicarbonate induced alkalization of the serum uncouples the drug from the myocardial sodium channels and provides a buffer that helps to prevent, or limit, acidosis that might follow a seizure or hypoperfusion.[6] The aim is to maintain arterial pH 7.45 to 7.55, ideal being 7.5.

Consider hypertonic saline for TCA toxicity if sodium bicarbonate is ineffective and pH of 7.45-7.55 has been reached. It is proposed that a high sodium load would overcome sodium channel blockage by the TCA without the adverse effects of alkalosis as seen with sodium bicarbonate. There is animal evidence to support the use of hypertonic saline (...Continued on page 5)

TCA Poisoning (...from page 4)

after other therapies have been maximized, however human evidence is limited to case reports.[5]

Lidocaine may also be considered when severe alkalosis and/or hyponatremia limit the effective use of sodium bicarbonate. It is proposed that lidocaine acts by competitively binding at the same site on cardiac sodium channels as TCAs.[8] Its fast association and dissociation allows displacement of TCA from cardiac cells resulting in increased repolarization time and QRS narrowing. Lidocaine should be considered particularly for TCA exposures with slower sodium channel recovery times such as amitriptyline and nortriptyline.[6,8]

A similar theory may be applied to phenytoin with its proposed mechanism of allosteric modulation of the TCA binding site.[8] However, phenytoin use in TCA toxicity remains shrouded in a cloud of uncertainty due to limited data, the risk of hypotension and its narrow therapeutic index. Phenytoin is not currently recommended by experts in the field.[8]

Lastly, lipid emulsion has been postulated to reduce toxicity by creating an intravascular lipid compartment into which lipid-soluble drugs may be sequestered and/or enhance free fatty acid metabolism.[5, 6] Animal studies and case reports suggest that life-threatening arrhythmias that are not corrected with sodium bicarbonate may respond to infusion of lipid emulsion.

TCA Overdose - Pharmacological Management Pearls

Indications for rapid sequence induction (RSI)

TCA overdose delays gastric emptying and may cause vomiting, increasing aspiration risk, particularly in patients with reduced level of consciousness. A low threshold for early intubation should be adopted and the need should be continually reassessed.

Gastric decontamination and extracorporeal treatments

Activated charcoal may be considered for use within 1 hour of TCA ingestion but only in patients with an intact or secured airway. Methods to enhance elimination of TCAs such as manipulation of urinary pH, hemodialysis or hemoperfusion are not indicated due to high protein binding and large volumes of distribution of TCAs.[3]

Hypotension

TCA overdose causes hypotension by reducing preload and afterload as well as direct effects on the myocardium. Optimizing the preload may reverse hypotension. This may be achieved by a bolus of intravenous fluid. Sodium bicarbonate may reverse hypotension even in the absence of acidosis and is indicated if hypotension is persistent.

Arrhythmias

Maximal ECG changes usually observed within 12 hours of ingestion and generally take 24-48 hours to resolve.[4] Administration of sodium bicarbonate, even in the patient without acidosis, may reverse TCA-induced arrhythmias. ECG abnormalities QRS prolongation (> 100 ms) and right axis deviation are associated with increased risk of cardiac arrhythmias. The use of sodium bicarbonate should be strongly considered in this situation.

Sodium bicarbonate

For life-threatening toxicity use sodium bicarbonate IV bolus. The dose can be repeated followed by a continuous infusion with blood gas monitoring to a target pH of 7.45-7.55.

Seizures

Prolonged seizures should be treated initially with benzodiazepines. If there is no response to benzodiazepines, RSI should be considered.

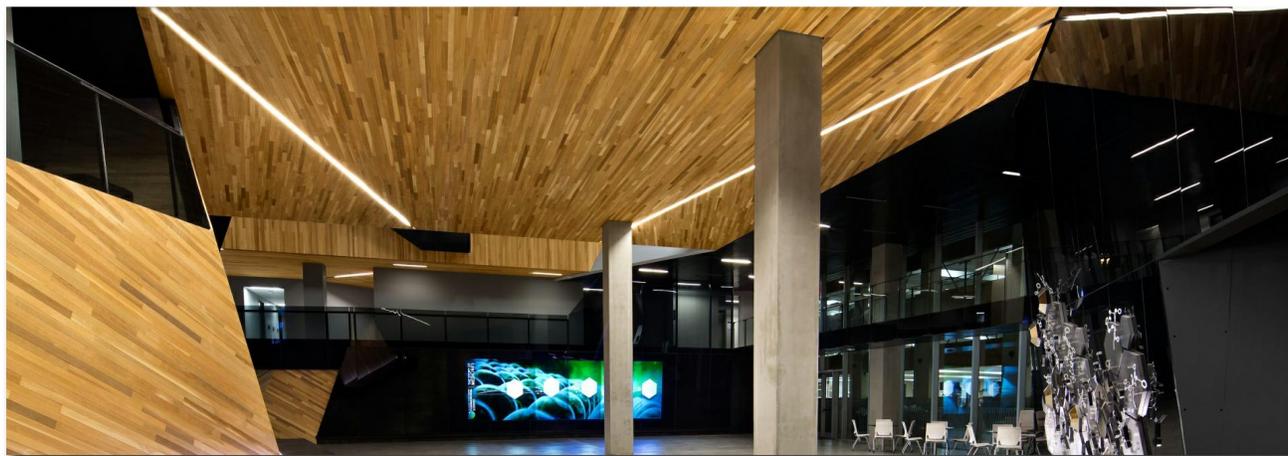
ECG monitoring

ECG monitoring is essential for all patients at moderate/high risk. Serial 12-lead ECG recording is recommended in all patients to monitor for changes in QRS duration.

Table 1 – Adapted from Guidelines in Emergency Medicine Network (GEMNet) for TCA overdose 2011.[5]

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Inside the new Faculty of Pharmaceutical Sciences Building at UBC

Buprenorphine in Pregnancy and Lactation (...from page 3)
Reported relative infant doses range from 0.09–1.9%.^[19]
As with any infant breastfeeding while the mother is taking narcotics, the infant should be monitored for any signs of adverse effects including sedation and apneas.^[19]

There is no published data on naloxone and lactation, however, due to its negligible oral bioavailability it is considered compatible with breastfeeding.^[19] Therefore, the combination product of buprenorphine/naloxone (Suboxone®) is also considered compatible with breastfeeding.^[19]

To prescribe Suboxone® in British Columbia, physicians must hold an exemption to prescribe methadone for opioid dependence and must have completed an online education module available at www.suboxonecme.ca.^[20]

Suboxone® was added to the BC provincial hospital formulary in 2014 with restrictions for use that mirror restrictions set in the community for coverage by Pharmacare; Suboxone® can be used in patients where methadone is contraindicated or where there is an inadequate response or intolerance to methadone.^[21] Suboxone® is available onsite for use at BC Women's Hospital from the pharmacy department.

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Research, Education & Awards

Karen Ng, BScPharm, PharmD, BCPS

Research

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Awards

Dr. Dean Elbe was awarded the Lower Mainland Pharmacy Services Residency Program **Veteran Preceptor of the Year** for 2014-15, recognizing his excellence in teaching, precepting, and mentoring residents.

Dr. Karen Ng was awarded the Lower Mainland Pharmacy Services Residency Program **New Preceptor of the Year** for 2014-15, recognizing her excellence in teaching, precepting, and mentoring residents.

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