Updates from C&W Pharmacy, Therapeutics & Nutrition (PTN) Committee
Jennifer Kendrick, BScPharm, PharmD

The C&W PTN 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.

**Backorders and Product Changes:**
We are currently facing shortages of many essential medications. The Pharmacy Department continues to monitor supplies and usage. We appreciate all of the assistance in reviewing options to mitigate these shortages.

- **Epinephrine** injectable has been on backorder. The 30 mg/30 mL vials are available again and have been restocked on the wards. The 1 mg/1 mL ampoules remain on backorder.
- **Heparin 10 unit/mL** is on backorder and pharmacy is compounding the product in the interim.

**Drug Dosage Handbook Updates**
The 7th Edition of the Pediatric Drug Dosage Guidelines was published in 2018. Since printing, the following monographs have been updated:

- **Acyclovir:** correction to dosing listed in comments section
- **Cefixime:** new monograph
- **Cloxacillin:** updated dosing for cystic fibrosis
- **Daptomycin:** new monograph
- **Dimenhydrinate:** updated dosing for children and adults
- **Ganciclovir:** correction to treatment dosing
- **Piperacillin/tazobactam:** updated dosing for cystic fibrosis
- **Pregabalin:** removal of restriction to the acute pain service and addition of dosing for younger children
- **Procaaine:** updated dosing for SVT
- **Sodium phenylbutyrate:** monograph missing from print version

**PDM updates continued…**
- **Fentanyl:** IV intermittent administration shortened
- **Glucarpidase (SAP):** added information for use in methotrexate intoxication
- **Hyaluronidase (SAP):** new monograph
- **Hyoscine butylbromide:** addition of IV direct route
- **Icatibant:** new monograph
- **Levocarnitine:** continuous IV infusion added as a route, as this is given in parenteral nutrition
- **Mephenytoin:** geographic restriction for IV intermittent removed
- **Methylprednisolone High Dose (pulse) Therapy:** methylprednisolone expiry extended to 24 hours
- **Nelarabine:** new monograph
- **Nivolumab:** new monograph
- **Pegasparaginase:** no longer Special Access Programme medication
- **Piperacillin/tazobactam:** clarified piperacillin vs. tazobactam content under the reconstitution section and maximum concentration
- **Potassium for Oncology Guideline:** this is a PDM policy that supplements the potassium monograph. It was updated to reflect current standards and practice for concentrated electrolytes.
- **Sufentanil:** new monograph
- **Sugammadex:** new monograph
- **Temsirolimus:** new monograph
- **Thiotepa:** no longer Special Access Programme medication
- **Trimethoprim/sulfamethoxazole:** updated to include additional compatibility and dilution instructions
- **Vasopressin:** updated to allow for administration outside of critical care. Monitoring parameters added.
- **Vinorelbine:** updated with information about flushing the line after the dose

**BCWH Parenteral Drug Manual**
Tranexamic acid – new monograph

**Pre-printed Orders**
Clinical Informatics and the PTN Committee have been busy with developing, updating, and approving C&W pre-printed orders have been approved since the last edition of the Pharmacy Informer. All order sets are posted on the C&W Intranet on ePOPs (intranet)

**Policies & Procedures**
Policy & Procedure Updates are listed on page 2

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**Get Informed**

In this Issue:
- PTN Committee Updates...[Page 1]
- Research Publications...[Page 2]
- Beta-Lactam Cross-Reactivity...[Page 3]
- Methylphenidate ER Generics...[Page 5]
- MMR vaccine Update...[Page 6]
- Pharmacy Awareness Month 2019...[Page 6]
- Informer Editorial Board...[Page 6]
The Treatment of Acute Asthma Nurse Initiated Activity (NIA) Policy and Algorithm have been updated to allow nurses to give oral corticosteroids for the purpose of treating moderate to severe asthma in a patient with previously diagnosed asthma in emergency care settings. Previously, only salbutamol and ipratropium could be administered in this NIA. This change reflects the current Registered Nurses’ scope of practice in BC.

The BCCH Inpatient Asthma Guidelines were developed to standardize inpatient management of asthma and to facilitate weaning of bronchodilator therapy.

The BCCH Inhaled Medication Challenge for Children with Cystic Fibrosis with Spirometry and without Spirometry were developed to standardize the management of children undergoing inhaled medication challenges.

The Urology Surgical Prophylaxis Guidelines were developed by Urology and Antimicrobial Stewardship and provide guidance on timing, choice, and dose of antibiotics for a number of urological procedures.

The Perforated Appendicitis Pathway was developed by Surgery and Antimicrobial Stewardship. Once daily metronidazole and ceftriaxone is now a treatment option.

The Influenza Guidelines (aka BCCH Algorithm for Oseltamivir Treatment of Influenza in Children and Youth) were updated for 2018/2019 to remove the lower age limit of 2 weeks.

Guidelines for the Administration of Intranasal Fentanyl were updated to remove the geographic restrictions (previously restricted to Emergency Department and Medical Day Unit).

The Guideline for the Administration of Propofol for Migraine Treatment in the ED was approved.

The Methadone Prescribing and Administration Policy for Women’s Hospital was updated to allow hospital prescribers to continue patients’ home methadone without a full methadone exemption.

The Guidelines for Administration of Methadone for Weaning Opioids for PICU were updated to reflect current processes and information (e.g. contraindications and precautions).

The PICU Palliative and End-of-Life Care Guidelines provide detailed guidance for management of pain and other symptoms in palliative patients.

The Eating Disorders Intensive Treatment Service Inpatient Unit: Hypoglycemia Protocol for children and adolescents WITHOUT Diabetes Mellitus was approved.

The Naloxone for Opioid Overdose Nurse Independent Activity was developed for nurses in Child and Youth Mental Health to administer naloxone for opioid overdose and includes a decision support tool.

The NICU Probiotic Guideline was updated to clarify exclusion criteria and precautions, as well as to reflect the change in brand name of the probiotic.

The Delegated Medical Act – Administration of medications by Nuclear Medicine Technologists was developed as part of a Lower Mainland Policy to allow nuclear medicine technologists to administer select medications after completing an education program.

The Penicillin and Beta Lactam Allergy Management Guideline was developed by Antimicrobial Stewardship.

Several Children’s Hospital medication administration policies were updated: Intramuscular Injection Policy and Enema Administration Policy.

Several PT&N Policies were updated as per the 3 year review policy. They can be found on ePOPS under the PT&N Committee Manual.

Research Publications
Jennifer Kendrick, BScPharm, PharmD


Paquette V, Elwood C. The safety of oral fluconazole therapy in pregnancy. CMAJ 2019:191:E177-E178. Citation


Beta-lactam allergies, particularly allergies to penicillin, are over reported. Though beta-lactam allergy assessments are an important step in determining if a patient has a true allergy. Unnecessary avoidance of beta-lactam antibiotics and use of alternative non-first line antibiotics has been associated with increased patient morbidity including decreased effectiveness, increased adverse effects, longer hospital stays, and increased *C. difficile* infection rates. Alternative non beta-lactam antibiotics are often more expensive and broader spectrum and exposure can lead to colonization and infection with resistant organisms.\[1,2\]

Historically, cross reactivity rates between classes of beta-lactam antibiotics have been over estimated and based on studies with flawed methodologies. However, as allergies have become better defined and the role of the antibiotic chemical structure on likelihood of cross reactivity is better understood, more recent data suggests cross reactivity between penicillins and other beta-lactams is much lower.\[3\] For patients in which a true penicillin or other beta-lactam allergy cannot be ruled out based on history and assessment, the below information can be used to aid in determining which beta-lactam may be safe to administer.

**Note:** This information is not meant to replace clinical judgement or meant to be an antibiotic treatment guideline. The information below is based on the most recent literature surrounding beta-lactam cross reactivity and is meant as an aid in determining beta-lactam alternatives with a low cross allergy risk. It is important to note that new intolerances (i.e. any allergy or adverse reaction reported in a drug allergy field) can occur after 0.5 to 4% of all antimicrobial courses depending on the specific agent. Expect a higher incidence of new intolerances in patients with three or more prior medication intolerances.\[4\] A thorough allergy assessment should always be conducted in any patient reporting an allergy.

**Patient has a Penicillin Allergy:**

Penicillins are a group of antibiotics and include: penicillin, ampicillin, amoxicillin, cloxacillin, piperacillin-tazobactam

Cross reactivity between the penicillins and cephalosporins is primarily due to similarities in side chains and not similarities in the beta-lactam ring structure. If a patient has a true penicillin allergy, a cephalosporin with different side chains can be safely administered.\[4-6\] Note cepafizolin does not share a similar side chain with any other beta-lactam commonly used in Canada. Please refer to the cross reactivity chart on the next page (Figure 1) to determine if cross allergy is possible between beta-lactams.

Cross reactivity between penicillins and carbapenems is very low. Carbapenems would be a reasonable option when antibiotics are required in patients with an allergy to penicillins.\[13,14\]

**Patient has a Cephalosporin Allergy:**

Unlike the penicillins, cross reactivity between the cephalosporins is typically not a class effect. Cross reactivity in cephalosporins is primarily based on the similarities between the structures’ side chains. Therefore, if a patient has a cephalosporin allergy, one can safely be given a different cephalosporin (or other beta-lactam) that has dissimilar side chains.\[9\] Note cepafizolin does not share a side chain with any other beta-lactam commonly used in Canada. Please refer to the cross reactivity chart on the next page (Figure 1) to determine if a cross allergy is possible between beta-lactams.

...continued on page 4

**References**

**IMPORTANT NOTE:** this document and chart can only be used to evaluate the risk of cross reactivity between beta-lactams in patients with type I IgE mediated hypersensitivity reactions. This does NOT apply to type II, III, and IV hypersensitivity reactions. Please see Figure 2 for information on other types of hypersensitivity reactions and their management.

### Figure 1: Beta-Lactam Cross Reactivity Chart [7,11,12,13,15,16]

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
<th>Mediator</th>
<th>Onset</th>
<th>Clinical Reactions</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>IgE mediated, immediate type hypersensitivity</td>
<td>IgE antibodies</td>
<td>0 – 1 hr</td>
<td>Anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritus</td>
<td>Avoid offending agent and cross reacting agents (see Figure 1)</td>
</tr>
<tr>
<td>Type II</td>
<td>Antibody dependent cytotoxicity</td>
<td>IgG and IgM antibodies</td>
<td>greater than 72 hr</td>
<td>Hemolytic anemia, thrombocytopenia, Neutropenia</td>
<td>Drug specific, avoid offending agent</td>
</tr>
<tr>
<td>Type III</td>
<td>Antibody complex mediated hypersensitivity</td>
<td>Antigen-antibody complexes</td>
<td>greater than 72 hr</td>
<td>Serum sickness, vasculitis, drug fever, glomerulonephritis</td>
<td>Avoid beta-lactams, consult AMS or ID for alternative antibiotic</td>
</tr>
<tr>
<td>Type IV</td>
<td>Delayed type hypersensitivity</td>
<td>T cells</td>
<td>greater than 72 hr</td>
<td>Contact dermatitis, some morbilliform reactions, severe exfoliative dermatoses, (e.g. SJS/TEN), AGEP, DRESS/DiHS, interstitial nephritis, drug-induced hepatitis</td>
<td>Avoid beta-lactams, consult AMS or ID for alternative antibiotic</td>
</tr>
</tbody>
</table>

**Key:** X – beta-lactam antibiotics that have a similar structure/side chains and indicate a risk for cross reactivity

![Beta-Lactam Cross Reactivity Chart](image-url)

**Figure 2. Coombs and Gell Classification of Hypersensitivity Reactions [17,18]**
Methylphenidate Extended-Release Formulations: What’s Under the Hood?

Dean Elbe, BScPharm, PharmD, BCPP
Reviewed by Ryan Chan, MD, FRCPC
Medical Director, BCCH ADHD Clinic

Four subsequent market entry (i.e., generic) methylphenidate extended-release (ER) formulations comparable to the original branded medication (Concerta®) for treatment of attention deficit/hyperactivity disorder (ADHD) have become available in Canada over the past few years.[1-3] Understanding the characteristics of the delivery systems, pharmacokinetics and how these parameters may impact clinical effectiveness can help prescribers, pharmacists and patients make informed therapeutic decisions.

The reference methylphenidate ER formulation (Concerta®), first marketed in 2000, uses the trademarked Osmotic [Controlled] Release Oral [Delivery] System (OROS).[4] The OROS tablet has an immediate-release overcoat, containing 22% of the labelled amount of methylphenidate; the remaining 78% delayed-release portion is inside the tablet, split between two compartments each with a different concentration.[4,5] As water from gastric juices enters the tablet via a semi-permeable osmotic membrane, a polymer (called the push layer) expands and presses against the drug layers, causing drug to be expelled from the tablet at a controlled rate via two laser-drilled holes located at one end of the tablet.[4,5] The higher drug concentration in the middle layer results in an “ascending” release profile producing proportionately higher serum methylphenidate levels in the afternoon and early evening.[5] This release pattern attempts to overcome desensitization of dopamine receptors in the prefrontal cortex following initial exposure to methylphenidate, which can result in intraday tolerance to the stimulant effects.[5] The expected duration of action following a dose of Concerta® appropriate for age and weight is 10–12 hours.[4,6]

Health Canada bioequivalence standards for the majority of generic drug formulations focus exclusively on two pharmacokinetic parameters: the “area under the concentration versus time curve to the time of the last quantifiable concentration” (AUCₜ) and the “mean maximum drug concentration” (Cₘₐₓ) in single-dose crossover comparative bioavailability studies conducted in healthy adults.[7] To be deemed bioequivalent, the Cₘₐₓ of the generic formulation must be between 80%–125% of the reference product, and the 90% confidence interval of the mean AUCₜ of the generic formulation must be between 80%–125% of the reference product.[7] Perhaps somewhat surprisingly, the time when the Cₘₐₓ occurs (called Tₘₐₓ) is not a parameter in the definition of bioequivalence.

All four Canadian methylphenidate ER generics are formulated as compressed sustained-release tablets, and do not employ OROS or any alternate osmotic delivery system.[1-3] While the AUCₜ and Cₘₐₓ of all three generic products are within Health Canada’s tolerance limits, the Tₘₐₓ occurs several hours earlier compared to Concerta®[Table 1].[1,3] This means serum methylphenidate levels from the generic formulations start to decline several hours earlier, which may limit the ability of these formulations to overcome intraday tolerance and potentially lead to a shorter duration of action.

Generic drugs are typically not required to undergo efficacy trials, so there are no published trials evaluating any of the generic methylphenidate ER formulations in children or adolescents.

A six-week randomized, double-blind crossover satisfaction study comparing equal doses of Concerta® and Teva- (formerly Novo) methylphenidate-ER-C was conducted in 20 adults with ADHD.[8] Participants were more satisfied in terms of efficacy and side effects while being treated with Concerta® compared to an equivalent dose of Teva-Methylphenidate-ER-C.[8] All participants chose to continue Concerta® at study end.[8]

The differences in release profiles between the reference product and the generics appears to be clinically significant, with multiple reports of alteration in therapeutic response following substitution of one of the generic formulations for Concerta®.[9,10] In addition, generic methylphenidate ER formulations can more easily be divided, crushed and powdered, which potentially increases their abuse potential.[11] While Concerta® is not abuse/diversion-proof, it is more difficult and less convenient than most other psychostimulant formulations to extract the drug powder from the tablets.

Due to the pharmacokinetic differences between formulations and the lack of clinical evaluation of the generic formulations in children and adolescents, only Concerta® is a first-line treatment recommendation in the Canadian ADHD Resource Alliance (CADDRA) ADHD Practice Guidelines, Fourth Edition.[6]

Pharmacists are allowed to independently undertake product selection for generic substitution, but should consider and discuss the above factors when making substitution decisions or advising patients and families about methylphenidate ER products. For some patients, starting treatment with a generic formulation and titrating up to a dosage that provides a reasonable duration of action may be acceptable. Differences between products may be most noticeable when patients stabilized on one formulation are switched to a different formulation. A shortened duration of action is the most common complaint documented in adverse reaction reports following a switch to a generic methylphenidate ER product.[10]

...Continued on page 6

### Table 1

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters of Canadian Methylphenidate ER products*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance (54 mg tablet)</strong></td>
</tr>
<tr>
<td><strong>AUCₜ (% of reference)</strong></td>
</tr>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>ACT-MPH-ER[7]</td>
</tr>
<tr>
<td>APO-MPH-ER[8]</td>
</tr>
<tr>
<td>PMS-MPH-ER[9]</td>
</tr>
</tbody>
</table>

| **Cₘₐₓ (% of reference)**                                      |
| Reference                                                      | 106%  |
| ACT-MPH-ER[7]                                                 | 115.7%|
| APO-MPH-ER[8]                                                 | 83.44%|
| PMS-MPH-ER[9]                                                 | 110.1%|

<table>
<thead>
<tr>
<th><strong>Tₘₐₓ</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta® [4]</td>
</tr>
<tr>
<td>ACT-MPH-ER[7]</td>
</tr>
<tr>
<td>APO-MPH-ER[8]</td>
</tr>
<tr>
<td>PMS-MPH-ER[9]</td>
</tr>
<tr>
<td>TEVA-MPH-ER-C[10]</td>
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<table>
<thead>
<tr>
<th><strong>Half-life (t½)</strong></th>
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<tbody>
<tr>
<td>Concerta® [4]</td>
</tr>
<tr>
<td>ACT-MPH-ER[7]</td>
</tr>
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</tr>
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</tr>
<tr>
<td>TEVA-MPH-ER-C[10]</td>
</tr>
</tbody>
</table>

Table reproduced with permission from Elbe, D. Pharmacy Practice+Business, 2017;4:9-10.

*AUCₜ—area under the concentration versus time curve to the time of the last quantifiable concentration; Cₘₐₓ—mean maximum drug concentration; MPH—methylphenidate; Tₘₐₓ—time when the Cₘₐₓ occurs

* Conducted as separate bioequivalence studies in fasting adults with 54 mg single dose

$ In a 54 mg single-dose study of Concerta in children 7–12 years of age, Tₘₐₓ occurred at 9.1 h [4]

† Tₘₐₓ and t½ values for Concerta shown are from the Teva-MPH-ER-C product monograph bioequivalence study [3]
MMR Vaccine Reconstitution and Administration

Vanessa Paquette, BScPharm, PharmD

The standard order for the Measles-Mumps-Rubella (MMR) Live Virus Vaccine is 0.5 mL via subcutaneous injection in both children and adults. The vaccine is supplied by the pharmacy department as a lyophilized powder and diluent for reconstitution.

After the diluent has been added to the vaccine powder, the total resulting volume may be over 0.5 mL (usually 0.5 – 0.7 mL). It is important to administer the entire volume of reconstituted product to ensure the patient gets the full appropriate dose. Please do not discard any portion of the vaccine product.

For full product details, MMR immunization schedules, and timing of administration between the MMR vaccine and other live vaccine and blood products, please refer to the MMR vaccine monograph in the BCCDC Immunization Guidelines.

Generic methylphenidate ER formulations cost approximately 30% less than Concerta® for the same labelled dosage strength. BC Pharmacare currently covers the cost of generic methylphenidate ER formulations as a benefit in children 6 to 18 years of age, following submission of a Special Authority form for ADHD medication coverage (section A). [Link to form]

When filling a prescription for Concerta® at BC community pharmacies, the patient/caregiver is responsible to pay the difference in cost between the brand and generic formulation. Codes are available from innovator-sponsored programs that cover the differential cost for families who prefer to use Concerta® (or are prescribed Concerta® with “no substitution”).

Other extended-release methylphenidate products approved in Canada for use in children and adolescents (Biphentin®, Foquest®) are not eligible for Pharmacare coverage/Special Authority.

The BC Children’s Hospital Pharmacy Department continues to stock Concerta®, For patients taking a generic methylphenidate ER formulation who are admitted to hospital, and whose caregivers prefer to maintain use of the same formulation, the generic methylphenidate ER may be ordered and identified by the pharmacy for use during their admission, in accordance with the Patient’s Own Medications policy. [Link to policy] (intranet)

C&W Pharmacy Staff Members celebrate Pharmacy Awareness Month at our display in Shaughnessy Cafeteria

Thank you for participating in another fantastic year of Pharmacy Awareness! We celebrated Pharmacy Awareness Month from March 11 to March 15 and hosted a second information booth at the Atrium near Second Cup for the first time, in addition to our display in the cafeteria. There were numerous exciting activities including: pharmacy trivia, photo booth, Guess the Jelly Bean contest, and more. We really appreciate your enthusiasm and cannot wait to do this again. See you all next year!

Concerta Generic Formulations… continued from page 5

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References
3. Teva Canada Limited. Teva-Methylphenidate ER-C (methylphenidate hydrochloride extended-release tablets) product monograph. Toronto, ON: October 4, 2016. (note: product was formerly referred to as Novo-Methylphenidate-ER-C) Product Monograph

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The Editorial Board wishes to thank Karen Ng and Sharon Ho for their service and contributions to prior editions of the Pharmacy Informer. With this edition, we welcome new Editorial Board members Vanessa Paquette and Jason Tan.

BCCDC Immunization Guidelines