npcurrent
Canadian Journal for Nurse Practitioners

2020
ISSUE 6

Urticaria
The role of antihistamines

HIV Prevention
PEP in primary care

Caring for the Carers
Selfcare for nurse practitioners

npcurrent

A Canadian Journal for Nurse Practitioners

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5420 Highway 6 North, Suite 434
Guelph ON N1H 6J2
www.npcurrent.ca

ISSN 2561-8059

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npcurrent
Canadian Journal for Nurse Practitioners

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Real World Experience: Bilastine and Urticaria

Dr. Lyn Guenther
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Earlier this year, a real-world case project was published on the 2nd generation antihistamine bilastine (Blexten, Aralez Pharmaceuticals) and its' application in treating allergic conditions that require an antihistamine.

The following review is written by one of the authors of this paper, Dr. Lyn Guenther, with a focus on the treatment of urticaria, commonly referred to as hives, and a common presenting complaint in primary care.

Urticaria and Impact on Quality of Life

Urticaria, commonly referred to as hives, is a common occurrence in primary care practices given a lifetime prevalence of ~15-25%.[1,2] Urticaria can be classified by duration (acute < 6 weeks or chronic ≥ 6 weeks)[1,2] and by absence (spontaneous) or presence (inducible) of triggers such as pressure, cold, heat, exercise, vibration, or sun exposure.[2] Patients can experience both spontaneous and inducible urticaria.[2] In up to 50% of chronic spontaneous urticaria (CSU) cases, angioedema is present with or without wheals.[3] CSU has a significant impact on patients' quality of life with disruptions in home, work and school life.[4,5] In a study of 142 patients with chronic urticaria, 56% of the 103 working patients had lost at least 1 day of work due to urticaria.[6] Of the total study population, 63% suffered from anxiety and 46% worried that their disease would worsen.[6] CU had a negative impact on patients' self-image and attitude towards others.[6] Many felt less attractive, self-conscious and embarrassed.[6]

Marked sleep disruption was reported by 38% while an additional 54% had some interference with sleep.[6]

Guideline Treatment Recommendations

The Canadian Society of Allergy and Clinical Immunology (CSACI) recently published a position statement recommending that the use of 1st generation antihistamines (AH) such as diphenhydramine be discontinued and replaced with 2nd generation AHs for the treatment of urticaria.[7] The recommendation against 1st generation AHs is based on their potential side effect profile including: sedation, impairment with decreased cognitive function, poor sleep quality, dizziness and orthostatic hypotension.[7] The 2nd generation AHs are efficacious with an improved safety profile due to reduced sedating and anticholinergic effects.

Current international guidelines provide a treatment algorithm for urticaria and

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recommend initial treatment with a 2nd generation AH.[3] If adequate control is not achieved after 2-4 weeks or symptoms are intolerable, increasing the dose of the AH is recommended (Figure 1). Once an additional medication is considered, such as omalizumab, referral to a specialist should be made.[3]

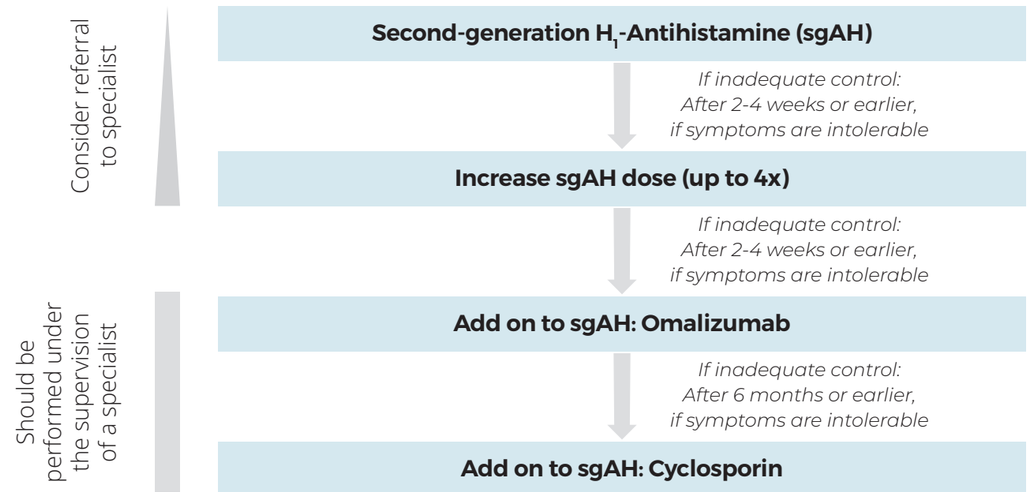
Case Studies with Bilastine

Bilastine was recently explored in real world cases by a panel of experts in Canada to manage both allergic rhinitis and urticaria.[8]

The results demonstrated patients achieving good symptom relief and tolerability over long periods.[8]

Bilastine is a 2nd generation antihistamine, available in Canada since 2017. Bilastine does not cross the blood-brain barrier, is not metabolized and does not interact with the cytochrome P450 system.[9] Bilastine can be prescribed without adjustments to patients with both renal and liver impairment. In clinical trials, the rate of somnolence with bilastine was 4.4%, equivalent to patients using placebo.[9]

Figure 1. Global urticaria guideline EAACI/GA²LEN/EDF/WAO



A short course of glucocorticosteroids may be considered in case of severe exacerbation.

EAACI - European Academy of Allergy and Clinical Immunology; GA²LEN - Global Allergy and Asthma European Network; EDF - European Dermatology Forum; WAO - World Allergy Organization

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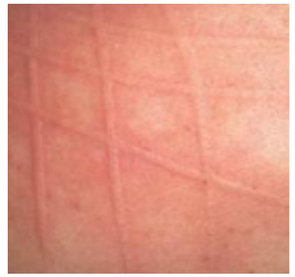
CASE

32-year-old woman with 6-month history of itchy red urticarial papules. The itch often woke her up at night. She could not identify any triggers. She tried Benadryl 25 mg - 100 mg[1-4] at bedtime with some improvement of itch and sleep, but developed a dry mouth and found it hard to wake up in the morning and concentrate at work. She was in otherwise good health and on no routine mediations.

Physical examination showed scattered red urticarial lesions with flares. Angioedema was not present, but symptomatic dermatographism could be elicited. (Figure 2)

Figure 2. Dermatographism elicited with a toothpick



She was switched to bilastine 20 mg at bedtime. After 1 week, she was less itchy with fewer hives. After 2 weeks, the dose was increased to 40 mg at bedtime and her urticarial lesions, dermatographism and pruritus resolved. She did not have any somnolence, dry mouth or difficulty concentrating while on bilastine, even with the higher dose.

Consideration to tapering of the antihistamine should be given if a patient has been lesion and symptom free for 2 weeks. If there is a flare, the previous dose should be given.

Comment:

This patient had chronic (lasting 6 or more weeks) spontaneous (no triggers) as well as inducible (symptomatic dermatographism) urticaria. Patients with urticaria should be assessed for dermatographism particularly since many of them, as in the case of this patient, are not aware that they have it.

She had anticholinergic adverse effects including dry mouth, sedation and inability to concentrate with the first generation antihistamine diphenhydramine (Benadryl®). Her urticarial lesions, itching and dermatographism cleared with twice the approved dose of a second-generation antihistamine, bilastine.

First generation antihistamines such as diphenhydramine should not be used to treat urticaria. They are associated with many adverse effects including dry mouth, sedation and inability to concentrate.[7] Second generation antihistamines such as bilastine are much better tolerated. If control is not adequate with a once-daily second generation antihistamine, the dose can be increased up to 4 times.[3] This patient only required a doubling of the dose for skin and symptom clearing.

A study in patients with cold contact urticaria showed increased efficacy (based on critical temperature thresholds) with two-fold and four-fold updosing of bilastine without sedation.[10] In addition, a small crossover, randomized, double-blind, placebo-controlled study in healthy volunteers showed that the wheal and flare surface areas after histamine injection were inhibited significantly more with bilastine 20 mg than desloratadine 5 mg and rupatadine 10 mg. Bilastine also had the fastest onset of action.[11]

Summary

Urticaria is a condition most NPs in family practice are likely to encounter and presents significant concerns for patient's quality of life.[4,5,8] Recent guidelines from the CSACI recommend against the use of 1st generation AHs (e.g. diphenhydramine) due to their significant side effect profile.[7] The most recent international urticaria guidelines recommend initial treatment with 2nd generation AHs and increasing the dosage of a single 2nd generation AH before considering adjunct therapy.[3,7] Real world cases with bilastine have demonstrated how patients with urticaria can be treated to provide relief and improved quality of life.[3,8]

> "Real world cases with bilastine have demonstrated how patients with urticaria can be treated to provide relief and improved quality of life.[3,8]"

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PEP for primary care

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ABSTRACT

HIV prevention now involves pre-exposure and post-exposure prophylaxis, known as PrEP and PEP. While literature about how nurse practitioners can provide PrEP exists, there is none for PEP. This paper summarizes what is known about PEP and provides guidance for nurse practitioners who wish to include this intervention in their practice.

Introduction

While HIV prevention has historically focused on persons avoiding practices that transmit HIV, such as needle sharing and condomless sex, prevention now includes chemoprophylaxis, including pre- and post-exposure prophylaxis; known as PrEP and PEP, respectively, these interventions involve giving antiretroviral medications to HIV-negative patients.[1-3] Due to these changes, nurse practitioners' work has expanded; whereas previous prevention efforts mostly focused on counselling about testing and HIV transmission, they now include PrEP, for which guidelines exist.[1,2] Although PEP guidelines for nonoccupational HIV exposures also exist,[2,3] this intervention is less discussed in the primary care literature, despite being an important part of comprehensive HIV prevention services. This paper thus (1) includes a review of both the research on PEP and the CDC[3] and Canadian[2] PEP guidelines, and (2) serves as a starting point for nurse practitioners to consider how to integrate HIV PEP into their practice.

What Evidence Supports PEP?

The evidence on PEP mostly arises from animal model studies involving macaques, and shows that, when antiretroviral medications are administered to monkeys after parenteral or mucosal exposure, there are marked reductions in HIV seroconversion.[4,5] These studies also identified the required timing for PEP: fewer seroconversions occurred when PEP was administered as soon as possible after exposure, ideally within 24 hours, and continued for 28 days; shorter courses and later starting times corresponded with higher seroconversion rates.[6] One case-controlled trial using one antiretroviral medication (AZT) among humans subsequently identified an 81% reduction in seroconversion among hospital employees (primarily nurses) who were exposed to HIV via needlestick.[7] This high level of prevention made it unethical to withhold PEP in future studies. Data about maternal-child transmission further supported the utility of PEP, showing that PEP administration during childbirth correlated with less vertical transmission.[8,9] The outcome

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of these studies is that PEP is now standard-of-care for HIV exposures.

One limitation to PEP access is that, despite knowing it is effective, it remains mostly only available in emergency rooms and sexually transmitted infection (STI) clinics. While these settings are appropriate because STI clinic nurses have specialized knowledge and emergency rooms are always open, limiting access to these sites defies what is known about PEP: i.e., the time from HIV exposure to administering the first dose of PEP is centrally important to its effectiveness. It thus makes sense that the first dose of PEP could be administered in primary care settings where patients might present for care. Guidance about how to do this is detailed below.

Does my patient need PEP?

Based on available research, PEP is given to HIV-negative persons as soon as possible after HIV exposure.[2,3] As such, when considering PEP, the nurse practitioner's first step is to determine eligibility, which can occur by posing the following questions:

- Did the potential exposure to HIV occur within the preceding 72 hours?
- Was the potential exposure sufficient to cause HIV transmission?
- Is the person who may need PEP HIV-negative?
- Is the source of the potential exposure HIV-positive?

If the answer to any of these questions is no, PEP is not warranted. The time period has elapsed, the risk of transmission is minimal, the patient for whom PEP is being considered does not require it because s/he/they are already HIV-positive, and/or the source person is HIV-negative. Often, the timing and exposure questions are easily answered. Nurse practitioners need only ask patients about what occurred when. Although patients will not always provide these details (due to, for example, substance use or a reluctance to disclose), activities considered high-risk for HIV transmission include needle sharing and needlestick, condomless anal sex (receptive and penetrative), and condomless vaginal sex (receptive higher risk, but penetrative still an at-risk practice).[1,2,3] In contrast, determining the patient's and source person's HIV-status is often less clear, leaving nurse practitioners to decide if patients are likely HIV-negative and if the source person is potentially HIV-positive.

Is my Patient HIV-Negative?

To determine the patient's HIV-status, a three-part approach can be used. First, recent results should be sought. Although HIV results may not be valid due to testing window periods and ongoing risk, these results do reduce the period of potential new infection. Even a test from one year ago shortens the period of uncertainty to the time since testing plus the window period, which is 12 weeks for third-generation antibody tests and about 6 weeks for fourth generation antigen-antibody tests.[10] Second, if available, nurse practitioners should perform point-of-care HIV testing, with a positive result precluding PEP. In an STI clinic, this procedure identified patients who were unaware they were HIV-positive when seeking PEP.[11] This is unsurprising, considering that recent CDC[12] and Canadian[13] estimates suggest that about 14% of persons living with HIV are undiagnosed. Third, nurse practitioners should assess patients for symptoms of seroconversion, including fever, chills, malaise, arthralgia, myalgia, rash, lymphadenopathy, abdominal pain, nausea, vomiting, and/or diarrhea.[1] Although up to 75-80% of persons experience these symptoms 10-28 days post-exposure, their presence does not preclude PEP initiation, as they are non-specific.[3] The presence of such symptoms may warrant more frequent testing to rule out seroconversion.

Although test results confirming an HIV-negative status with the last potential exposure being outside the window period would be ideal, due to the importance of initiating PEP quickly, nurse practitioners should prescribe PEP without delay for patients who are potentially HIV-negative. According to the CDC[3], when results are not available or are limited by window periods, decisions about PEP should be "based on the assumption that the potentially exposed patient is not infected". If tests determine otherwise, expert consultation should be sought, and discontinuation versus continuation of PEP at this point should occur under the guidance of an HIV specialist.[3]

One unique situation nurse practitioners may encounter is when patients who use PrEP request PEP. In this case, nurse practitioners should first assess patient's medication use; PEP is not indicated if the patient takes PrEP as prescribed. The CDC[3] is explicit on this point, stating that PEP is only indicated if the patient takes PrEP "sporadically" or not at all "within the week before recent exposure". Because this recommendation is only based on expert opinion, another option, based on the pharmacokinetic data of PrEP medication which shows a 72 hours intracellular half-life, is to provide PEP when all other conditions for PEP are fulfilled and the patient misses two consecutive pills.[14] While this approach has a lower threshold for PEP initiation, it more cautiously ensures PEP usage in the absence of evidence for when and how to use PEP in patients who are taking PrEP. It may, however, be needlessly conservative.

Is the Source Person HIV-Positive?

For the source's HIV-status, a few strategies can be used. The first is to test the source person and determine his/her/their HIV-status.[2,3] If positive, viral load and genetic testing should occur.[3] The outcome of such results raises the point of the *undetectable equals untransmittable* ("U=U") campaign, which is built on a robust body of evidence showing that HIV transmission becomes virtually zero once a person attains and sustains an undetectable viral load, which is <40-400 copies of HIV per mL of blood.[15] An important caveat in this body of work is that persons must actually have undetectable viral loads. Indeed, although no HIV transmissions occurred in a recent study about U=U, 55 participants were excluded from analysis because they did not maintain an undetectable viral load; these 55 patients constituted 5.5% of the entire study sample (n=1004) and 47.4% of those excluded (n=116).[16] In another study from San Francisco,[17] "Of the 118 HIV-positive men on ART, 92.4% reported they were virally suppressed at last clinic visit, 62.4% were actually virally suppressed as indicated by blood tests, and 77.8% of their partners reported that they believed their HIV-positive partner was virally suppressed". Thus, while a truly suppressed viral load would likely not warrant PEP, without the nurse practitioners being able to confirm such a viral load, it would be prudent to initiate PEP. If an undetectable viral load is confirmed later, PEP can be discontinued.[3] The same approach should be adopted for patients who report that their partner is HIV-positive, but confirmation of the viral load is not available.[2] In such cases, assume that a potential for transmission exists, and discontinue PEP later as needed.

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Alternatively, the patient may inform the nurse practitioners that the source person reported being HIV-negative, which is susceptible to the same limitations that apply to the patient's HIV test results. Another consideration is that the patient's assessment of HIV-negative status may be based on perceptions of the partner's appearance and social standing.[18] The nurse practitioners should thus inquire about how patients know their partners' HIV-status. Statements such as "he looked clean" and "he said he was on PrEP" may be uncovered, and are contextual interpretations of HIV-status, not explicit statements about HIV-status by the source person.[18]

> "…PEP is indicated for HIV-negative patients who had exposures that transmit HIV with persons who are either known to be HIV-positive with detectable viral loads or unconfirmed undetectable viral loads or members of high-risk groups with unknown or reportedly negative HIV-status.[2,3]"

Without direct confirmation of the source person's HIV-negative test results, PEP should be given if the risk of HIV transmission is enough based on what occurred and the risk of HIV exposure is sufficient, with HIV prevalence being a proxy measure for this level of risk. Following WHO[19] definitions, the HIV epidemic in the United States and Canada is "concentrated" because there is a <1% HIV prevalence among pregnant women and a >5% prevalence among specific sub-populations; this contrasts with generalized epidemics where HIV prevalence is >1% among pregnant women. In the United States and Canada, therefore, groups with an HIV prevalence >5% are considered high-risk based on prevalence; this includes men who have sex with men, persons who inject drugs, and persons who are Indigenous, African, Caribbean, or Black, or transgender.[12,13] The same approach of determining potential risk of HIV exposure based on group-level HIV prevalence would apply if the patient did not know the source person's HIV-status.

In summary, PEP is indicated for HIV-negative patients who had exposures that transmit HIV with persons who are either known to be HIV-positive with detectable viral loads or unconfirmed undetectable viral loads or members of high-risk groups with unknown or reportedly negative HIV-status.[2,3] (Table 1)

How do I Prescribe PEP?

What Should I Prescribe and for How Long?

According to CDC[3] and Canadian[2] guidelines, a first-line PEP regimen for adults includes 28 days of oral Emtricitabine-Tenofovir DF (FTC/TDF) 200/300mg fixed dose tablet once daily plus oral Raltegravir 400mg twice daily. Alternatively, oral Dolutegravir 50mg once daily can be used instead of Raltegravir, but should be avoided in pregnant women due to the risk of neural tube defects.[3] Contraindications to FTC/TDF include nephrotoxicity and an estimated creatinine clearance <60mL/min; there are no drug-drug interactions.[3] The side effects of FTC/TDF include asthenia, headache, and gastrointestinal upset, such as nausea, vomiting, and diarrhea.[3] There are no contraindications for Raltegravir, although dosage adjustment (doubling to 800mg po BID) is required if the patient takes Rifampin.[3] Polyvalent-cation antacids and laxatives should also be avoided due to the potential for chelation.[3] Raltegravir side effects include "insomnia, nausea, fatigue, and headache; severe skin and hypersensitivity reactions are also possible".[3]

Because there are no randomized controlled trials evaluating PEP medication, which agents to use is based on expert opinion.[3] Those that were selected are chosen because they are tolerable, require minimal dosing schedules, and have few drug-drug interactions.[3] The combination of three agents is similarly extrapolated from studies involving HIV-positive patients, among whom three medications yield high levels of viral suppression and little risk of resistance.[3]

The next consideration regarding PEP relates to providing the medication. The simplest approach is to administer the first dose immediately on-site and dispense the remainder of the 28 days

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Table 1.

HIV-Status		Transmission Risk	Recommendation
Positive	Viral load unknown	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Viral load reportedly undetectable	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Viral load confirmed undetectable	High risk*	PEP not indicated
		Low risk†	PEP not indicated
Negative	Laboratory results confirmed	High risk*	PEP not indicated (depending on window periods)
		Low risk†	PEP not indicated
	Laboratory results unconfirmed (high prevalence group)	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Laboratory results unconfirmed (low prevalence group)	High risk*	PEP not indicated
		Low risk†	PEP not indicated
Unknown	High prevalence group	High risk*	PEP indicated
		Low risk†	PEP not indicated
	Low prevalence group	High risk*	PEP not indicated
		Low risk†	PEP not indicated

* High risk = percutaneous exposure (needlestick, needle sharing), anal sex (receptive/penetrative), vaginal sex (receptive/penetrative)

† Low risk = oral sex, spitting, biting, sharing sex toys

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of medication. This strategy corresponds with the fastest PEP initiation and the highest rates of continuation.[20] However, this approach requires that nurse practitioners both have PEP on-site and prescribe the full course of medication without follow-up or consultation before giving the full course of medication. Another approach is to provide a 3 to 6 day starter pack of medication, whether dispensed on-site or as a prescription to fill at the pharmacy, and have the remainder of the medication dispensed or given as a prescription once baseline laboratory results are available.[2] This approach ensures patient start PEP promptly, but only continue if it is were safe to do so. This approach also ensures a follow-up visit for PEP continuation, when the nurse practitioner can discuss side effects, adherence, and the results of the baseline testing; the nurse practitioner can provide additional supportive counselling at that time as well.[3] A third option is to provide a 3 to 6 day starter pack and refer the patient to an HIV specialist, as happens in many emergency departments. This approach might be ideal for nurse practitioners who are inexperienced with PEP, but requires multiple visits with multiple providers in multiple settings.[3] A fourth option is to send the patient to the local emergency department for immediate consultation with an infectious disease specialist. Examples of patients who would need to be referred out for management of PEP include: pregnancy, pediatrics, those with renal dysfunction (estimated creatinine clearance <60mL/min). Otherwise, provision of the full course of medication is within the scope of most nurse practitioners, and the first approach is the simplest for patients to obtain and continue PEP.

What Testing is Required?

In addition to HIV testing (ideally as a point-of-care and 4th generation serology test), nurse practitioners should test patients for whom PEP is considered for other bloodborne infections, such as syphilis, and hepatitis A, B, and C.[2,3] Hepatitis B testing, including surface antigen and surface antibody and core antibody, is important because FTC/TDF is partially active against hepatitis B infection and could induce reactivation in persons with active infection upon discontinuation.[2,3] Gonorrhea and chlamydia testing at urogenital, pharyngeal, and rectal sites should also occur, as indicated by the patient's practices.[2,3] Pregnancy testing should also occur as needed, even though pregnancy is not a contraindication to PEP.[2,3] Pregnant patients need only be given medications that are safe. (See above note about Dolutegravir.) Next, serum creatinine, alanine aminotransferase, and aspartate aminotransferase should be ordered to ensure patients can process PEP medication.[2,3] FTC/TDF is renally processed and requires an estimated creatinine clearance >60mL/min for use, and Raltegravir can cause elevated liver enzymes.[2,3] These serologic chemistry tests are ordered at baseline and repeated after two weeks if abnormal.[2] If the estimated creatinine clearance is <60mL/min, immediate consultation with an HIV specialist is required, so the patient can continue PEP with a non-renally processed medication. Otherwise, repeat testing after PEP completion is all that is required, and should include HIV testing using a fourth-generation test, unless follow-up is not guaranteed, in which case a point-of-care test could be used. The CDC[3] suggests this testing should occur after 4-6 weeks, and then after 3 and 6 months

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after PEP initiation. The Canadian guidelines[2], in contrast, recommend follow-up testing only after 3 months.

What Counselling Do I Provide?

Counselling is an essential component of PEP, and nurse practitioners should emphasize a few items. For one, patients need to be informed that PEP medications need to be taken everyday for 28 days.[2,3] Missing doses or not completing the course of medication undermines its efficacy. Next, nurse practitioners should ensure that patients are aware PEP can fail. Although current triple medication regimens likely have higher prevention outcomes than the 81% reduction in seroconversions identified in the single existing occupational case-control trial,[2] PEP failures still continue to occur.[21] Nurse practitioners should thus inform patients about the symptoms of HIV seroconversion and instruct them to return to clinic if such symptoms occur during, or up to one month after, PEP use.[2,3] Due to the risk of such failures, nurse practitioners should also instruct patients to eschew practices that transmit HIV until infection is ruled out after 6-12 weeks from the potential exposure that warranted PEP.[3] This approach would minimize onward HIV transmission in instances of PEP failure.

As another important item, nurse practitioners need to emphasize general risk reduction strategies for patients who request PEP. This would include a discussion about and the provision of condoms and sterile drug equipment, as well as discussions about HIV transmission and risk mitigation. As part of this, patients who warrant PEP should be offered PrEP. While the CDC[3] and Canadian[2] guidelines recommend PrEP after repeat instances of PEP use, other research has identified up to 10% seroconversion rates within one year after a single instance of PEP use, suggesting that multiple usages may not be required before initiating PrEP.[11,22] Following the CDC[3], provided that a patient has no contraindications to FTC/TDF and good adherence to PEP medication, s/he/they could initiate PrEP on the first day after completing PEP. Due to PEP failures, symptoms and missed pills may warrant expert consultation before proceeding with a PEP-to-PrEP transition, to reduce the risk of drug resistance. Otherwise, PEP-to-PrEP transitions can likely occur, and are included in the latest iterations of the CDC PEP[3] and PrEP[1] guidelines.

What Else Should I Consider?

Patients not known to be vaccinated for Hepatitis B should receive a single dose of vaccination at the time of PEP initiation.[3] Follow-up vaccination should be guided by baseline results. Hepatitis B immune globulin should also be provided if testing of the source person is possible and determines that this person is Hepatitis B antigen positive.[3] Moreover, patients who have negative pregnancy tests should be offered emergency contraception and ongoing contraception, as is appropriate and safe for them.[3]

Another important item is that, before providing PEP, patients need to know it exists and where to obtain it. Proactively, nurse practitioners should inform patients about PEP, especially those belonging to groups with elevated HIV prevalence, and, as part of this, instruct patients that they need to obtain PEP as soon as possible after potential HIV exposure, ideally within the first 24 hours, but up to 72 hours. The main message is that PEP should be initiated rapidly because it likely becomes less effective as time passes.

Closing Remarks

PEP is an important HIV prevention tool that is often restricted to specialized settings, such as STI clinics and emergency departments. This, however, does not need to be the case: primary care nurse practitioners can initiate patients on PEP and perform all relevant monitoring. This builds on current evidence about the importance of rapid PEP initiation and guidelines which emphasize the need to have such HIV prevention be more broadly available within the healthcare system. This paper serves as a tool for nurse practitioners to consider how to implement PEP in their practice. In doing this, primary care nurse practitioners can provide their patients with comprehensive HIV prevention services, and ideally link these patients with the most appropriate services in the most convenient locations.

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In the News

Current healthcare research

Mental health challenges four times higher in young mothers

The first study in Canada to use diagnostic interviews to assess mental health concerns beyond postpartum depression in young mothers shows that nearly two-thirds have at least one mental health problem, and almost 40% have more than one.

The Young Mothers Health Study compared 450 mothers under 21 with 100 mothers over 20 at time of first delivery. Age-matched mothers were also compared with childless 15- to 17-year-old girls who had been previously assessed for mental health concerns in the 2014 Ontario Child Health Study. Young mothers were found to be two to four times more likely to have an anxiety, conduct, or attention-deficit disorder than their childless peers or older mothers.

The report, published in the *Journal of Adolescent Health*, cites high risk and potential negative outcomes for their children as reasons to focus further on detection and treatment in young mothers as a group.

Lieshout, R. et al. The Mental Health of Young Canadian Mothers. Journal of Adolescent Health, 2020; 66(4): 464-469. doi:10.1016/j.jadohealth.2019.10.024

Skin cancer: men are genetically more prone

Findings of a study recently published in *Nature Cancer* point to specific gene mutations as a possible explanation for the higher incidence and lower survival rates of cutaneous melanoma observed in males.

Researchers examined genetic mutations in over 1,000 melanoma cases in order to identify significantly mutated genes (SMGs) that cause melanoma. Three SMGs were identified on the X chromosome; of these, one gene – RNA helicase DDX3X – showed loss-of-function mutations in males only.

It is not presently understood why some melanoma patients respond better than others to immunotherapy; emerging data indicates that sex differences may be involved. Better understanding in this area could help match melanoma patients with therapies that are most likely to best treat their specific case. Researchers are currently investigating whether the sex difference in mutations found in this study might be part of the solution to this ongoing question.

Alkallas, R., Lajoie, M., Moldoveanu, D. et al. Multi-omic analysis reveals significantly mutated genes and DDX3X as a sex-specific tumor suppressor in cutaneous melanoma. Nature Cancer 2020; 1(6): 635–652. doi:10.1038/s43018-020-0077-8

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In the News

Current healthcare research

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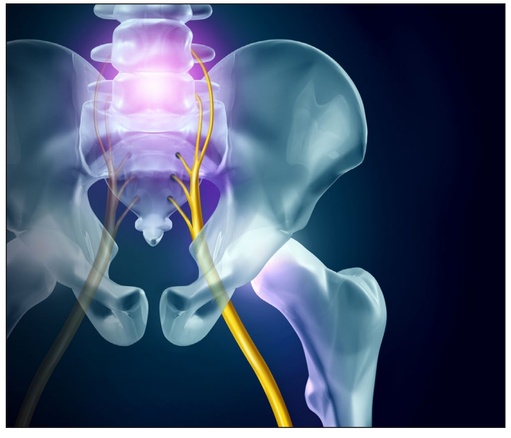

Improving outcomes for patients with sciatica

The first study to compare surgery and non-operative care for persistent sciatica has found that surgery results in better patient pain outcomes.

128 patients with sciatica lasting 4-12 months and lumbar disc herniation were randomly assigned to one of two groups. Patients in the surgical group underwent microdiscectomy; the nonsurgical group received 6 months of nonoperative care, including physiotherapy and medication. Leg-pain intensity was scored using a visual analogue scale from 0 to 10, with 10 being most intense.

The results, published in the *New England Journal of Medicine*, indicated baseline mean pain scores of 7.7 for the surgical group and 8.0 for the nonsurgical group. At 6 months, patients reported mean scores of 2.8 in the surgical group and 5.2 in the nonsurgical group, for a mean difference of 2.4. 34% of patients in the nonsurgical group eventually underwent surgery after the 6-month study period.

Bailey, C. et al. Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 12 Months. New England Journal of Medicine, 2020; 382(12): 1093-1102. doi:10.1056/nejmoa1912658

Immediate dialysis for patients with acute kidney injury no better than wait until-necessary approach, researchers find

A study published in the *New England Journal of Medicine* found that using an accelerated strategy of renal-replacement therapy (RRT) does not reduce the risk of death for patients.

The trial, which is the largest on this subject, randomly sorted nearly 3,000 critically ill patients with evidence of severe acute kidney injury (AKI) into two groups. In the accelerated-strategy group, patients received RRT within 12 hours of meeting eligibility criteria; in the standard-strategy group, RRT was not initiated until complications emerged or AKI persisted for over 72 hours.

At 90 days, 43.9% of patients in the accelerated-strategy group and 43.7% in the standard-strategy group had died (P=0.92). Of the surviving patients, 10.4% in the accelerated-strategy group and 6.0% in the standard-strategy group remained dependent on RRT, indicating a slightly higher occurrence of continued RRT dependency in accelerated-strategy patients.

Bagshaw, S. & Wald, R. et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. New England Journal of Medicine, 2020; 383(3): 240-251. doi:10.1056/nejmoa2000741

Game-changing blood test accurately detects Alzheimer's disease

Researchers have made a breakthrough in Alzheimer's disease (AD) detection: a blood test sensitive enough to detect the protein P-tau181, an AD biomarker, even in patients not showing signs of cognitive impairment.

The study, published in *The Lancet Neurology*, examined four clinic-based cohorts, which included: AD patients and age-matched controls; patients with other impairments; and healthy young adults. When blood test results were compared to those of cerebrospinal fluid (CSF) analysis and PET scans, the gold standard for AD detection, they were found to be highly similar.

Previously, expensive PET and invasive CSF were the only available detection methods besides autopsy; this discovery could make diagnosis significantly more accessible worldwide. It could also help stage AD and differentiate it from other neurodegenerative disorders; this is crucial, as about 30% of patients are currently incorrectly diagnosed. Additional trials are ongoing; the test is expected to be widely available in 2-3 years.

Karikari, T. et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: A diagnostic performance and prediction modelling study using data from four prospective cohorts. The Lancet Neurology, 2020; 19(5), 422-433. doi:10.1016/s1474-4422(20)30071-5

The COVID-19 Vaccine Status in Canada

Epidemiologists agree that to halt the spread of COVID-19, a complex disease caused by the novel virus SARS-CoV-2, the world needs a vaccine to create herd immunity. Scientists from multiple countries are banding together in an unprecedented fashion. They are partnering, sharing, cooperating and working around the clock to develop, test, review and eventually manufacture an effective SARS-CoV-2 vaccine with an acceptable safety profile. Since some vaccine candidates never get approved, it is prudent to have many get tested simultaneously in parallel development to increase our chances of protecting people from COVID-19. This is exactly what researchers are doing; researching as many vaccine candidate options as possible. As of August 18, 2020, there were over 139 vaccine candidates in the preclinical evaluation stage and 28 vaccines in human trials.[1] Typically, the time that it takes for a vaccine to go through clinical trials up to approval can take years. However, scientists and regulators all over the world are taking innovative steps to shorten that amount of time drastically. Canada is no exception as our researchers, and regulatory reviewers are taking actionable steps to speed up the arrival of an effective SARS-CoV-2 vaccine without compromising safety.

During a webinar focused on COVID-19 treatments and vaccines, Dr. Megan Bettle, the Director of the Centre for Regulatory Excellence, Statistics and Trials at Health Canada (HC), explained some of the strategies that are being used to expedite the time to approval of SARS-Cov-2 vaccines.[2] The greatest challenge that Health Canada faces right now is speeding up the approval of COVID-19 vaccines without compromising safety, efficacy and quality. The HC strategies to accelerate COVID-19 vaccine trials consist of review process changes, flexible clinical study designs and global partnerships with other regulatory bodies.

Health Canada clinical trial review process

HC is responsible for reviewing and determining if a study design meets the standard requirements to proceed with the study and if the final study results prove that the product is safe and effective. By following this rigorous process, the time between a product starting its clinical trials to eventually being manufactured and used in patients could take years. With an ongoing pandemic, we must act as quickly as possible. Therefore, to expedite the review process, teams of dedicated COVID-19 reviewers have been assembled and are focusing solely on COVID-19 clinical trial applications and

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The COVID-19 Vaccine Status in Canada

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data to facilitate speed and consistency within the regulatory process. Advice on the clinical trial proposal and design is provided to the manufacturer within 15 days or sooner, which cuts the usual time by half. HC expects to see extensive, controlled phase III vaccine trials. Most of the vaccine candidates that are entering phase III trials are planning on including approximately 30,000 participants. This results in a massive amount of data to review. Rather than wait for the final results, HC is accepting rolling submissions, meaning that as certain packages of data become available, HC will review them immediately one at a time. This allows HC to engage and ask questions early on, allowing the researcher to adjust the strategy as required. Not needing to wait until all of the data from the three phases of clinical trials are complete before starting the review process is expected to expedite the review process substantially.

HC has certainly had plenty of opportunities to put their revised review procedures to the test since, as of August 11, 2020, 55 trials for treatment or prevention of COVID-19 have been approved in Canada. This includes clinical trial proposals for repurposed pharmaceuticals, biologics, and convalescent plasma. Moreover, 2 trials of vaccines specific to SARS-CoV2 have been authorized in Canada. HC is not anticipating many phase III trials of vaccines to be conducted in Canada because there is currently not enough infection within the country to test a vaccine for efficacy. It is optimal for phase III trials to be implemented in jurisdictions with very high active case counts.

Flexible clinical studies design

Trial design adaptations could be a real game-changer when it comes to shortening the timeline from vaccine research to availability on the market. Although not used all that often, adaptative designs have been around for at least 25 years. They allow flexibility for pre-planned changes to be made midway through the clinical trial. The changes at stake could be adjusting the sample size, refocusing recruitment efforts based on the identification of the patients most likely to benefit from the vaccine, stopping the trial at an earlier stage due to successful outcomes, and various other factors involved in the study design. Allowing clinical trials to adopt an adaptive design helps to improve the efficiency in the implementation of the trial and to transition from one phase to another more rapidly.[3]

HC is recommending Phase I / II adaptive designs to support expedited vaccine development. For example, researchers can design their vaccine trial by staggering participant cohorts as long as there is an adequate safety review before moving onto the next group. The roll-out of the study can begin with a younger adult population aged 55 or less and then tap into a higher-risk population of older individuals. Adaptive trial designs seamlessly bring a product from an early phase into a later phase of the clinical trials.

The safety of the clinical trial participants remains the top priority. Therefore, despite the flexibility being allowed in adaptive clinical trial design, HC expects to see safety studies done in animals before any vaccine gets used in humans. However, certain animal studies can continue once some of the human studies have begun.

Global partnerships with regulatory bodies

SARS-CoV-2 vaccine clinical studies are taking place worldwide. As such, regulators at HC are collaborating with international regulatory groups. The goal is for all of the major regulators to take a similar approach to COVID vaccines. HC works with the International Coalition of Medicines Regulatory Authorities (ICMRA). The ICMRA consists of the major international regulators. They hold weekly discussions to discuss vaccine candidates and common evidence standards to ensure a common approach. HC is also a member of various world Health Organization (WHO) working groups focused on various clinical trial issues. In these groups, discussions can range from global vaccine trials to which animals are optimal to test for specific research objectives.

HC also has existing work-sharing mechanisms with the Australia-Canada-Singapore-Switzerland consortium. This partnership allows for work-sharing between the regulators of these countries, which creates efficiencies

in SARS-CoV-2 vaccine reviews. For example, all the regulators from this group can work together on a particular review which would allow the vaccines to be approved more quickly and to get approval within the national markets simultaneously. HC also works very closely with the Food and Drug Administration (FDA) of the United States and European Medicines Agency. All of these international regulators are engaging internationally to support regulatory alignment and develop a common approach to the development of COVID vaccines and treatments.

This level of international collaboration is unprecedented. Groups are reaching out to one another. Data is published very rapidly so that researchers can benefit from one another's learnings.

Canada's position in the SARS-CoV-2 vaccine race

Canadian scientists are playing an important role when it comes to the development of a SARS-Cov-2 vaccine. For example, the CanSino Biologics Inc. / Beijing Institute of Biotechnology vaccine candidate, Ad5-nCoV, is an Adenovirus Type 5 Vector that was discovered due to a Canadian-developed cell line known as HEK293.[4] Canada is also involved

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The COVID-19 Vaccine Status in Canada

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in the Ad5-nCov research, which is currently in phase II trials.[5] Moreover, a Canadian developer, Medicago Inc., currently has a plant-based vaccine candidate in research. The Medicago Inc. vaccine candidate is in phase I trials with GSK or Dynavax adjuvants. This study is also taking place in Canada. Phase II trials for this vaccine candidate is expected to begin in October 2020.

Canada has also arranged an agreement with two manufacturers whose SARS-CoV-2 vaccine candidates are currently in phase III trials; Moderna / NIAID[6] (mRNA-1273, a LNP-encapsulated mRNA) and BioNTech / Fosun Pharma / Pfizer[7] (BNT162b1, a LNP-mRNAs). Millions of doses are expected from both partners.

In conclusion, although Canadian scientists and regulators are taking various steps to expedite the SARS-CoV-2 vaccine development, safety remains the primary focus. As a first in the world of clinical studies, scientists everywhere are collaborating to help curb the pandemic. Together, we can find a SARS-CoV-2 vaccine that will bring us a step closer to returning to our everyday lives.

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2. CADTH, Webinar "Developing a COVID-19 Vaccine", August 12, 2020
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5. Canada, National. "The National Research Council Of Canada And Cansino Biologics Inc. Announce Collaboration To Advance Vaccine Against COVID-19 - Canada.Ca". Canada.Ca, 2020, https://www.canada.ca/en/national-research-council/news/2020/05/the-national-research-council-of-canada-and-cansino-biologics-inc-announce-collaboration-to-advance-vaccine-against-covid-19.html. Accessed 14 Aug 2020.
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Caring for the Carers?

Working in health care has taken on new dimensions since March when a global pandemic was declared. We have seen restrictions to what services we can offer to ensure our health system has the capacity needed for COVID-19 patients; restrictions on how we can engage with our clients with protocols shifting to not allow for family or support persons; restrictions on how we can engage with each other, colleagues and teammates, no longer able to share spaces or break times to debrief as we are accustomed. In a recent open letter published in the Journal of the American Medical Association, Dr. B. Trappey (2020) expresses how the once heroic act of being on the frontline has now become the mundane, and shares concerns about mustering the energy to do it all again in a second wave. His letter garnered a good deal of attention with many frontline workers sharing how his words resonated with them.

Closer to home, the CBC radio show host and emergency room physician, Dr. Brian Goldman, spoke with colleagues who've been working the frontline. They shared that they are similarly, feeling overwhelmed and worried about how long they can manage in the face of an ongoing pandemic. "We all feel like we're running on fumes" a physician's assistant in Toronto shared with Dr. Goldman (CBC, 2020). Zaka et al (2020) found that over 75% of medical staff and residents reported increased stress and have made a call for increased attention and resources directed toward the psychological health of frontline workers during this pandemic. There is also evidence from Canada's previous experience with a pandemic; having

worked through the SARS outbreak revealed ongoing concerns with mental health and wellbeing for nurses and other care providers (Maunder, 2006). Recent research with Canadian nurses is showing similar concerns with increasing incidence of stress, anxiety and symptoms of depression (Stelnicki, 2020).

Zaka et al (2020) point to the importance for systemic approaches to offering and supporting interventions to address the psychological health of health care providers. Likewise, Canadian surveys are identifying that nurses are wanting support at an administrative or systemic level (Stelnicki, 2020). While it is crucial to have the required resources for nurses and nurse practitioners to continue to safely provide care, nurses and medical staff have also identified the need for ongoing support for their mental health (Zaka et al; Shanafelt, 2020).

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Caring for the Carers?

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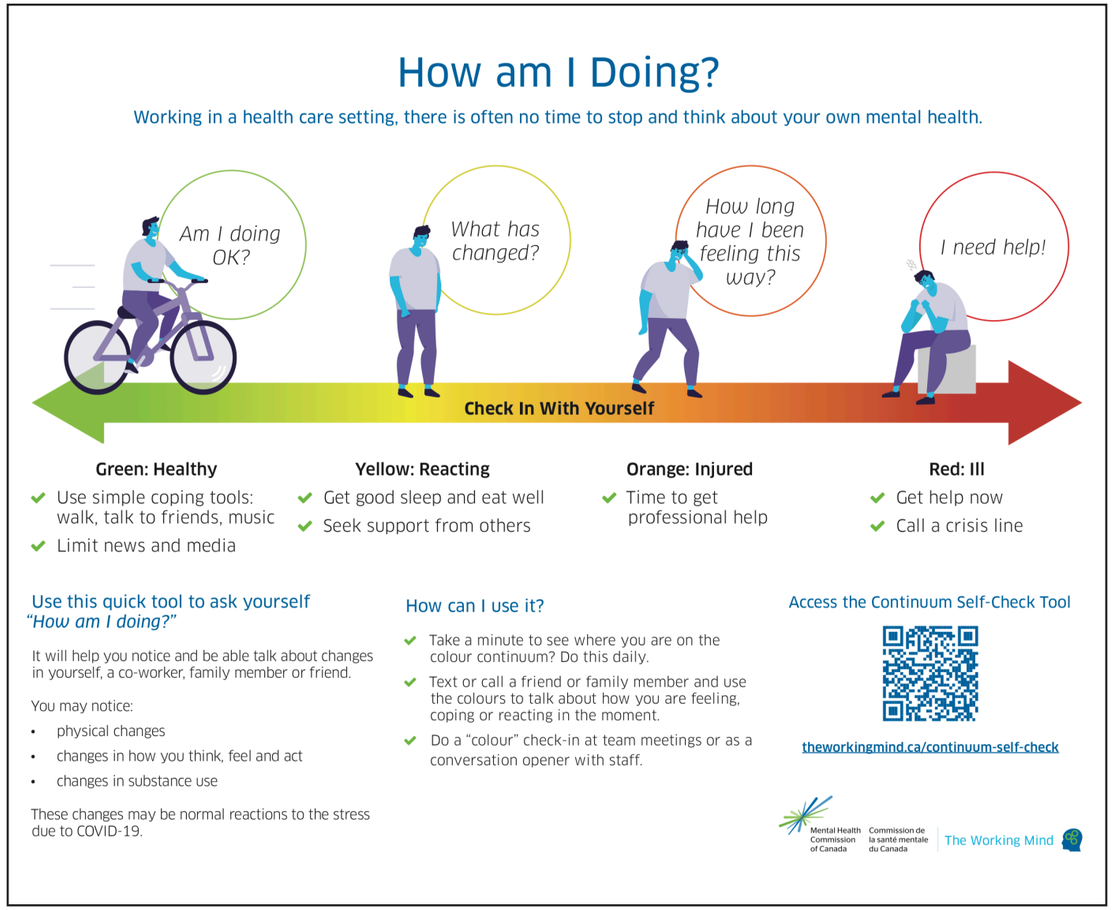
Maben and Bridges (2020) in a recent editorial reviewed the literature and made suggestions for a multi-faceted approach to supporting nurses' mental health and wellbeing during the pandemic. These include not only strategies at leadership and administrator levels, but also the importance of individual and peer support, and educational tools and training to facilitate that support.

As we move into the busy fall season with a second wave predicted, it will be more important than ever to tend to not just your physical health, but your mental health as well.



Below are some of the resources that have been developed to help support the mental health and wellbeing of health care providers as they face the daily challenges of working through a global pandemic.

We hope that you stay safe and healthy and that you are able to check-in not only with yourself but with your colleagues to ensure we all get through this together.

CBC Radio. White coat, Black art. Dr Brian Goldman, September 18, 2020

Maben J., & Bridges, J. (2020). Covid-19: Supporting nurses' psychological and mental health. Journal of clinical nursing. Advance online publication. https://doi.org/10.1111/jocn.15307

Maunder, RG, Lancee, WJ, Balderson, KE, et al. (2006) Long-term psychological and occupational effects of providing hospital healthcare during SARS outbreak. Emerging Infectious Diseases 12(12): 1924–1932.

Shanafelt, T., Ripp, J., Trockel, M. (2020). Understanding and addressing sources of anxiety among health care professionals during the COVID-19 pandemic. JAMA. Advance online publication. https://doi.org/10.1001/jama.2020.5893

Stelnicki, A. M., Carleton, R. N., & Reichert, C. (2020). Nurses' Mental Health and Well-Being: COVID-19 Impacts. Canadian Journal of Nursing Research, 52(3), 237–239. https://doi.org/10.1177/0844562120931623

Trappey BE. Running on Fumes. JAMA. 2020;324(12):1157–1158. https://doi.org/10.1001/jama.2020.17249

Zaka, A., Shamloo, S. E., Fiorente, P., & Tafuri, A. (2020). COVID-19 pandemic as a watershed moment: A call for systematic psychological health care for frontline medical staff. Journal of Health Psychology, 25(7), 883–887. https://doi.org/10.1177/1359105320925148

RESOURCES

https://www.espritautravail.ca/sites/default/files/how-am-i-doing-healthcare-poster-en.pdf

https://www.espritautravail.ca/sites/default/files/how-can-i-help-my-team-healthcare-poster-en.pdf

Canadian Resources:

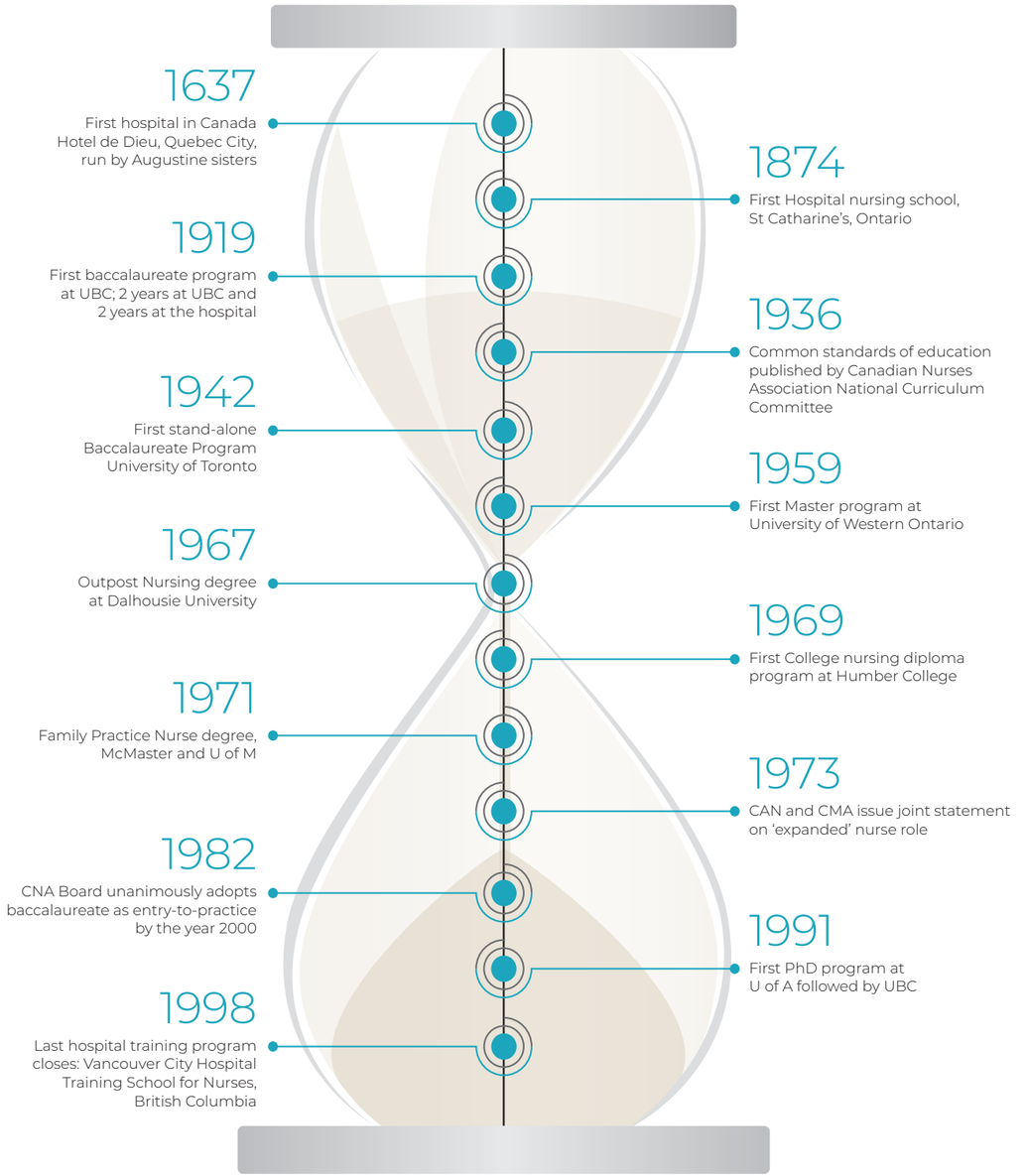
https://cmha.bc.ca/news/mental-health-resource-frontline-workers/

https://www.careforcaregivers.ca/events/

https://www.camh.ca/en/health-info/mental-health-and-covid-19/information-for-professionals

http://www.camh.ca/en/health-info/mental-health-and-covid-19/information-for-professionals/professional-support-groups

Milestones: History of nursing education in Canada*



* indigenous healers with knowledge of medicinal plants and traditional healing practices predate European settlers and occupied a critical role in the indigenous communities (Benoit & Carroll, 2005, p. 27). This chart represents a timeline of formal nursing education in Canada post colonization.

Benoit, C., & Carroll, D. (2005). Canadian midwifery: Blending traditional and modern practices. In C. Bates, D. Dodd, & N. Rousseau (Eds.), On all frontiers: Four centuries of Canadian nursing (pp. 27-41). Ottawa: University of Ottawa Press.

Baker, C., Guest, E., Jorgenson, L., Crosby, K. and Boyd, J. (2012) The evolution of education for professional nursing in Canada from the 17th to the 21st Century. CASN. https://www.casn.ca/wp-content/uploads/2016/12/History.pdf

Kaasalainen, S., Martin-Misener, R., Kilpatrick, K., Harbman, P., Bryant-Lukosius, D., Donald, F., ... & DiCenso, A. (2010). A historical overview of the development of advanced practice nursing roles in Canada. Nursing Leadership (Toronto, Ont.), 23, 35-60.

Wytenbroek, L., & Vandenberg, H. (2017). Reconsidering nursing's history during Canada 150. Canadian Nurse, 113(4), 16-18.

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References: 1. TYLENOL® Prescribing Information. McNeil Consumer Healthcare. May 10, 2017. **2.** Instar research, physician analgesic claims, 2015. **3.** *The Medical Post* and *Profession Santé* 2018 Survey on OTC Counselling and Recommendations.

* Please note that this content is not intended as professional medical or healthcare advice.