POSTER WRITING

1.

UNIVERSITY OF ALBERTA

Operating Lung Volumes and Dyspnea during Incremental Exercise in Asthmatics

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Background

Asthma is a chronic pulmonary disease characterized by recurrent episodes of bronchoconstriction, leading to wheezing and dyspnea.

Asthmatics have been shown to be less physically active than non-asthmatics[1,2], and the increased perceived dyspnea has been suggested to be a main reason asthmatics refrain from exercise[3].

While dyspnea during exercise is not believed to be explained by bronchoconstriction alone, abnormal changes in dynamic lung volumes during exercise have been suggested to play a role.

Exercise-induced expiratory flow limitation (EFL) is when the lungs try to breath past the maximal flow volume loop. This causes an increase in the time required to empty the lung, which does not fully allow the end-expiratory lung volumes (EELV) to return to baseline before the initiation of the next breath starts. To compensate for this the lungs will hyperinflate, and the inspiratory capacity (IC) will decrease[4]. Both EFL and a decrease in IC can lead to increased dyspnea[5].

It is currently unknown if there is a relationship between perceived dyspnea and operating lung volumes during incremental exercise in asthma. The results from this study could lead to better understanding of asthmatics are less physically active.

Purpose

The purpose of this study was to examine the operating lung volumes, the presence of EFL, and dyspnea in asthma compared to non-asthmatic controls.

It was hypothesized that asthmatics would exhibit a greater degree of EFL than controls, and that this would cause a reduction in IC...

Methods

Study Design: case – control study

Lung function at baseline
- Spirometry
- Lung volumes
- Diffusion capacity

Incremental exercise test to evaluate dynamic lung volumes
- Step Protocol: increase 25W/2 min
- Inspiratory capacity and dyspnea measure (10 point scale) at end of each stage   Borg
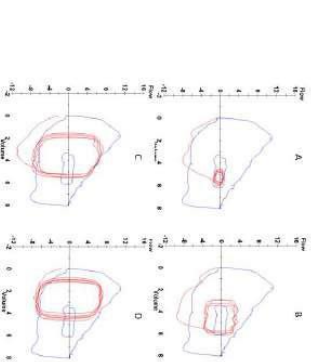- Total exhaustion termination

Fig 1. Tidal breathing during incremental exercise relative to the maximal Flow Volume Loop. A) Baseline tidal breathing B) 50% workload tidal breathing C) EFL during exercise D) Hyperinflation during exercise

Subject Characteristics

Table 1. Subject Characteristics. Values are expressed as means ± standard deviations. n=8

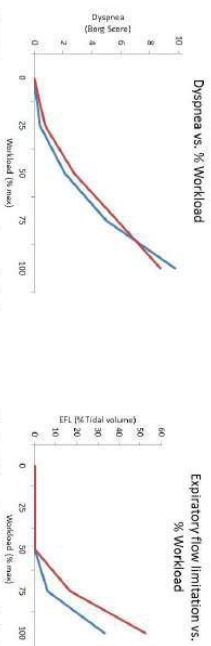|	Control	Asthmatic
Sex (M/F)	3,1	2,2
Age (yrs)	25±3	27±7
BMI (kg/m²)	27.0±4.0	25.3±4.4
FEV₁ pre (% predicted)	109.8±11.0	92.0±13.0
Baseline IC (L)	3.2±0.5	3.0±0.5
Absolute VO₂max (L/min)	3.3±0.5	3.5±0.7
Relative VO₂max (mL/kg/min)	38.9±4.2	43.8±2.5
Asthma Control Questionnaire	0±0	0.9±0.6

Results

Dyspnea vs. % Workload

Fig 2. Dyspnea score in asthma and controls during incremental exercise at baseline, 25, 50, 75, and 100% of max workload.

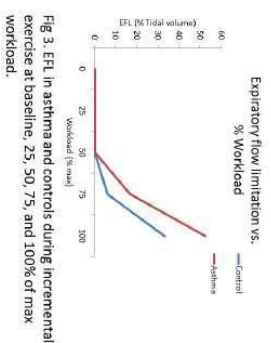Expiratory flow limitation vs. % Workload

Fig 3. EFL in asthma and controls during incremental exercise at baseline, 25, 50, 75, and 100% of max workload.
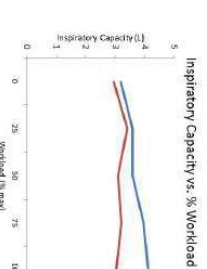

Inspiratory Capacity vs. % Workload

Fig 4. IC in asthma and controls during incremental exercise at baseline, 25, 50, 75, and 100% of max workload.

Conclusion

In conclusion, exercise expiratory flow limitation (EFL) is greater in those with asthma than controls. Inspiratory capacity (IC) is reduced with incremental exercise in asthmatics. Due to increased dyspnea and decreased IC in asthmatics we are able to assume that this could lead to increased dyspnea and exercise intolerance.

References and funding

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3. Mancuso CA, Sayles W, Robbins L, et al. Barriers and facilitators to healthy physical activity in asthma patients. J Asthma 2006
4. Stickland MK, Butcher SJ, Marciniuk DD, Bhutani M. Assessing exercise limitation using cardiopulmonary exercise testing. 2012
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The effect of chemotherapy and trastuzumab on skeletal muscle quality of breast cancer patients

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Introduction

- It has been identified that chemotherapy is metabolized in lean soft tissue, most of which is skeletal muscle (Carneiro, Mazurak, & Prado, 2016). Breast cancer treatment, especially chemotherapy, has been associated with weight gain. This increase in body weight is attributed to increases in fat mass, and decreases in lean mass (Gordon et al., 2011 and Kutynec et al., 1999).
- Studies using computerized tomography (CT) scans have found that patients with low skeletal muscle mass are more likely to experience treatment side effects and have a greater risk of overall mortality (Prado et al., 2009 and Villasenor et al., 2012).
- The use of magnetic resonance imaging (MRI) allows for reliable analysis of intramuscular fat, a measure of muscle quality, which may be a predictor of treatment side effects.

Objectives

1. Assess the reliability of MRI as a method to quantify changes in body composition in breast cancer patients.
2. To use MRI to characterize muscle quality and fat content changes over a 12-month period in HER2+ early stage breast cancer (EBC) patients.

Methods

Participants

- Participants were drawn from the MANTICORE (multidisciplinary approach to novel therapies in cardio-oncology research) study and were newly diagnosed HER2+ EBC patients, stages I to IIIA, receiving adjuvant treatment with trastuzumab (targeted therapy).
- Participants were excluded from the primary study about pharmacological protection from cardiotoxicity due to, baseline left ventricle ejection fraction <50%, history of heart failure, cardiomyopathy, or myocardial infarction, currently on heart failure medication, uncontrolled hypertension, prior chest radiation or chemotherapy, estimated glomerular filtration rate of <30ml/min/1.73m², or contraindications to MRI (Pituskin et al., 2016).
- Participants were excluded from this analysis of muscle quality if they were too large for the MRI scanner field of view, or had improperly localized MR images.
- For this preliminary analysis, the control group (i.e. usual care) from the MANTICORE study was analyzed.

Measurements

- Transverse MR images at the level of the third lumbar (L3) vertebrae were taken before, 3 months, and 12 months after chemotherapy and trastuzumab.
- A total of five 6mm thick slices were analyzed per time point using custom Matlab code to semi-automate tracings to separate subcutaneous, visceral, and muscular regions. The slices were centred around the middle of the L3 vertebrae.
- Within the skeletal muscle region, the different signal intensities for fat and muscle in a fat-water saturated image were used to quantify the amount of skeletal muscle and intramuscular fat.
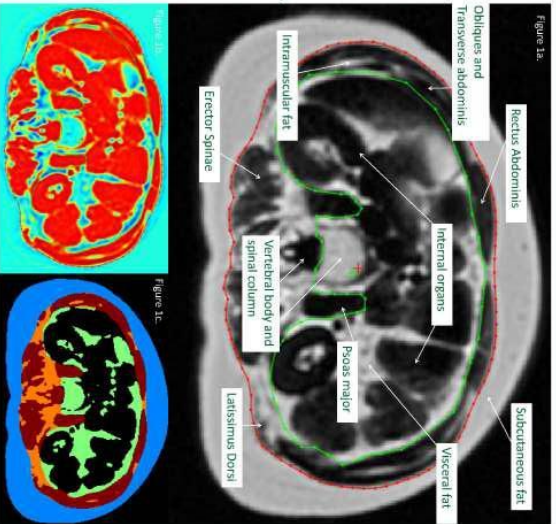

Figure 1a.

Figure 1b.

Figure 1c.

Figure 1. Illustrates the custom Matlab code used to create tracings around the subcutaneous, visceral, and muscular regions. 1a is the original fat-water saturated image with the red tracing separating subcutaneous from skeletal muscle, and the green tracing separating visceral from skeletal muscle. 1b is a water based tissue (red) and fat based tissue (blue). 1c is a colour map using signal intensities to separate the subcutaneous fat (blue), visceral fat (green), muscle (red), intramuscular fat (orange), while organs are black.

Results

Table 1. Baseline characteristics of the control group from the MANTICORE study (Pituskin et al., 2016).

Characteristics	Control Group
Age (years)	51 ± 7
Height (cm)	165 ± 7
Weight (kg)	71 ± 12
Breast Cancer Stage Number (%)	
1	14 (47)
2	6 (20)
3	10 (33)

Table 2. Percentage of total volume of subcutaneous fat, visceral fat, intramuscular fat and skeletal muscle at the L3 abdominal slice at baseline, 3 months, and 12 months.

Volume	Baseline (n=25)	3 months (n=25)	12 months (n=15)
Subcutaneous fat volume (%)	44.24±7.21	43.97±5.45*	45.69±6.47
Visceral fat volume (%)	26.80±6.29	27.11±5.85	26.69±5.32
Intramuscular fat volume (%)	7.73±2.59	7.68±2.21	8.05±2.32
Skeletal muscle volume (%)	21.23±5.41	21.24±5.36	19.57±5.02

*n=21; subcutaneous fat volume was excluded for three participants due to portions of fat being outside field of view.

Change in skeletal muscle volume

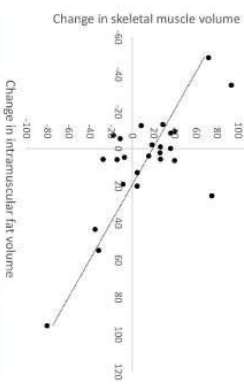Change in intramuscular fat volume

Figure 1. Correlation between change in intramuscular fat and skeletal muscle mass during chemotherapy (baseline to 3 months). r=25, r=0.72 (p<0.001).

- The coefficient of variation for inter-observer reliability was 1% for volume of subcutaneous fat, visceral fat, and skeletal muscle, and 7% for intramuscular fat.
- Overall, there were no statistically significant changes in volume for subcutaneous fat, visceral fat, intramuscular fat, or skeletal muscle at 3 or 12 months relative to baseline.
- There was a strong negative correlation (r=-0.72, p<0.001) between change in skeletal muscle and intramuscular fat during the first three months of chemotherapy.

Discussion

Reliability

- To our knowledge this is the first study to use MRI to quantify muscle quality or fat distribution in EBC patients.
- This preliminary analysis has shown that MRI is a reliable method to assess muscle quality and fat distribution based on inter-observer reliability.

Muscle Quality

- Other studies using dual x-ray absorptiometry or CT scans in similar populations have typically reported an increase in fat mass and either no change or a decrease in lean body mass (Battisti et al., 2014, Kutynec et al., 1999). No studies assessing intramuscular fat were identified.
- In this study, there were no statistically significant changes in fat and skeletal muscle volumes, indicating that muscle quality does not change during chemotherapy and trastuzumab treatment.
- This analysis illustrated a strong negative correlation between change in skeletal muscle and intramuscular fat demonstrating that a decrease in skeletal muscle mass occurs concurrent to an increase in intramuscular fat.

Limitations

- This preliminary analysis had a small sample size with a large range of values resulting in non-significant changes over time.
- Fat water suppressed images were used for this analysis, so any retention of water or inflammation was indistinguishable from lean mass. This may have resulted in skeletal muscle volumes appearing larger than the true value.

Future Considerations

- In the future, we plan to extract treatment outcomes from these patients' clinical records to determine whether muscle quality is a stronger predictor for chemotherapy toxicity than skeletal muscle mass depletion alone.

Conclusion

- Further analyses are needed to determine the mechanisms responsible for changes to intramuscular fat and skeletal muscle during chemotherapy treatment.
- A larger sample size is required to determine what changes to muscle quality occur.

My Role

- I analyzed the images acquired for the MANTICORE study for this preliminary analysis of muscle quality in EBC patients.
- I helped to acquire the inter-observer reliability for this analysis.
- I also performed a literature review on body composition changes in breast cancer patients.

References:
Battisti S. et al. (2014). Clinical Breast Cancer, 15(5), 365-370.
Carneiro I.P. et al. (2016). Current Oncology Reports, 18(62), 1-11.
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Pituskin E.N. et al. (2016). Journal of Clinical Oncology, 1, 1-7.
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Villasenor A. et al. (2012). Journal of Cancer Survivorship, 6, 398-406.

Making Better Prostheses: A New, Superior Evaluation System

Kovic, O., Lavoie, E.B., Valevicius, A.M., Boser, Q.A., Crockett, E., Hoehn, B., Mathewson, K.W., Vette, A.H., Pilarski, P.M., Hebert, J.S., and Chapman, C.S.

University of Alberta

UNIVERSITY OF ALBERTA — ACE Lab — ACTION IN COMPLEX ENVIRONMENTS — BLINC — DARPA DEFENSE ADVANCED RESEARCH PROJECTS AGENCY

Introduction

Body-powered prosthesis

"Double Amputee Controls DARPA Robotic Prosthetic Arms With His Mind"
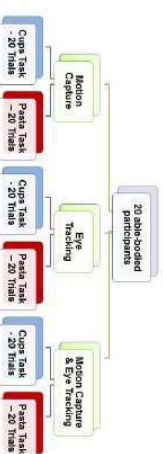
A Prosthetic Arm That Gives Amputees the Sense of Touch

- Huge technological advances, but no proper evaluation
- **Problem:** very expensive and life-changing devices with high rejection rates (~40%) [1]

Objectives

- Developing more sensitive measures of prostheses' effectiveness using simple, functional, everyday tasks
- Combining eye and motion tracking to study the relationship between visual attention and body movements
- Comparing able-bodied performance to bypass and prosthetic users
- Creating easy-to-use prosthetics evaluation system, which stimulates research into better prostheses, more accepted by users
- **Predictions:** 1. prosthetic users look more at the hand, because they lack sensory feedback and depend heavily on visual information; 2. eyes lead the hand significantly more in able-bodied than bypass and prosthetic users; 3. eye tracking is not changed when collected simultaneously with motion, and vice versa.

Methods

- 20 able-bodied individuals
- 3 experimental conditions: eye tracking only, motion capture only, simultaneous eye tracking and motion capture
- 2 functional tasks: Pasta Box task and Cups task
- 20 trials in each task, in each condition = 120 trials/participant = 2400 trials in total
- Randomized order of conditions to prevent equipment confounds

Dikablis Professional Eye Tracker

Scene camera

Pupil camera

Dilab pupil detection

Pasta Box Task

Crosshairs

Dikablis scene camera view

Cups Task

Nexus visualization

20 able-bodied participants		
Motion Capture	Eye Tracking	Motion Capture & Eye Tracking
Cups Task – 20 Trials	Cups Task – 20 Trials	Cups Task – 20 Trials
Pasta Task – 20 Trials	Pasta Task – 20 Trials	Pasta Task – 20 Trials

Bypass prosthesis

Current work & Preliminary results

- Post-processing of the normative data
- Calibrations and corrections of eye and motion tracking, AOI creation, etc
- Preparing the data for the analysis
- Selection of metrics of interest (e.g. gaze duration and location, joint angles, movement velocity, etc.)

Cups Task: Segment Durations

Reach, grasp, transport, release

Mean duration

Between subjects standard deviation

- Joint Kinematics (trunk, shoulder, elbow, wrist, grip aperture)
- End effector trajectory
- Eye behavior metrics (fixations, transitions, etc.)

Movement 1 Movement 2 Movement 3 Movement 4

Home
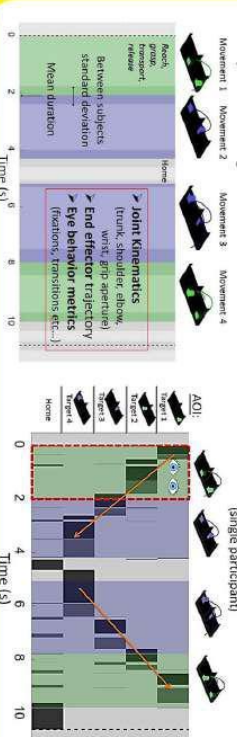
Area of Interest (AOI) % fixation
(single participant)

AOI:
Target 1 Target 2 Target 3 Target 4 Home

Preliminary 3D Gaze Vector model showing anticipatory saccades
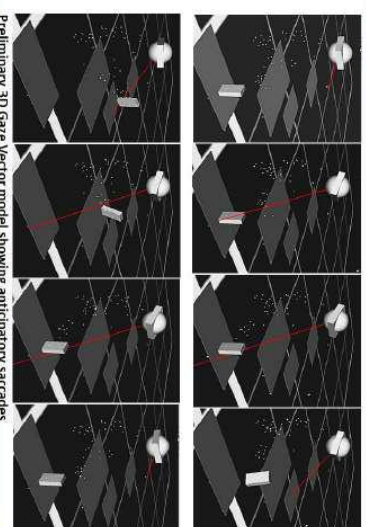
Future work

- Development of 3D Gaze Vector
- Validation of measurement system:
  - Bypass users
  - Prosthetic users
- Comparison to able-bodied participants' performance
- Creating an easy-to-use evaluation system for clinicians to assess prosthesis use in patients

References

1. Biddiss, E., Beaton, D., & Chau, T. (2007). Consumer design priorities for upper limb prosthetics. Disability and Rehabilitation: Assistive Technology,2(6), 346-357.

Sequential and spatially distributed neuromuscular electrical stimulation to reduce rapid contraction fatigue

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Human Neurophysiology Laboratory, University of Alberta

INTRODUCTION

- Neuromuscular electrical stimulation (NMES) can generate muscular contractions for individuals with motor impairments to improve muscle strength, mass and function.
- NMES is limited by rapid contraction fatigue due to higher firing frequencies of muscle fibers compared to voluntary contractions.
- Sequential NMES (sNMES) was designed to reduce fatigue by using multiple electrodes where stimulation pulses are rotated between electrodes, one after another.
- sNMES therefore reduces the frequency delivered to each electrode and thus muscle fiber firing frequency while still generating a fused contraction

Fig 1. Conventional NMES **(A)** and sNMES **(B)** pulse timing (Sayenko et al., Eur J Appl Physiol (2014) 114:793 - 804).

A Channel 1 ———————————40 impulses / sec (40Hz)

B Channel 1 —— 10 impulses / sec (10Hz)
Channel 2 —— 10 impulses / sec (10Hz)
Channel 3 —— 10 impulses / sec (10Hz)
Channel 4 —— 10 impulses / sec (10Hz)

OBJECTIVE & HYPOTHESIS

Objective: Investigate whether type of stimulation, conventional NMES (NMES) or sNMES, and electrode placement, collocated (NMESc) or over motor points of the quadriceps (NMESs), affects fatigue in the quadriceps during NMES.

Hypothesis: Fatigue will be greatest in NMESc, followed by NMESs and sNMESc. Fatigue will be least in sNMESs after a fatigue protocol.

METHODS

NMES was applied over the quadriceps in 4 participants (2 females and 2 males aged 28.9 ± 8.1 years).

Fig 2. NMESc **(A)** and NMESs **(B)** electrode placements used in fatigue protocol. **(C)** Biodex apparatus used to measure isometric knee extension torque.

A   **B**   **C**

METHODS

Determine stimulation intensity which generates a 15% MVC train.

stim.
sNMESs   sNMESc   NMESs   NMESc

15% MVC

Fatigue protocol: 170 contractions in 3 min, initial contraction = 15% MVC NMES delivered at 40Hz, 0.3 sec "on", 0.7 sec "off"

sNMESs   sNMESc   NMESs   NMESc

Outcome measures:

Fatigue = Torque of last binned contractions / Torque of first binned contractions

Δ MVC
Pre MVC(Nm) – PostMVC(Nm)

2 × 2 ANOVA with repeated measures

RESULTS

A   **B**

C   **D**

Fig 3. Torque during fatigue protocols delivered using sNMES and NMES and the collocated electrode placement **(A)** MVCs before (solid line) and after (dotted line) the fatigue protocols **(B)** Fatigue **(C)** and reduction in MVC **(D)** in a single participant.

Fig 4. Group torque data (n=3) during a fatigue protocol. Each point represents data averaged over 5 consecutive contractions.

Normalized Torque

Bin Number

sNMESs   sNMESc   NMESs   NMESc

Fig 5. Group fatigue data (n=3) after a fatigue protocol.

Fatigue

sNMESs   sNMEc   NMESs   NMESc   sNMES   NMES

Fig 6. Reduction in MVC (n=3) after a fatigue protocol.

Δ MVC (Nm)

sNMESs   sNMEc   NMESs   NMESc   sNMES   NMES

CONCLUSION

- Fatigue was significantly less during sNMES than NMES, however, there was no significant difference in the reduction of MVC.
- The similar decline in MVCs, but greater decline in torque during the NMES fatigue protocols suggests some of the NMES fatigue is due to mechanisms proximal to the neuromuscular junction.
- There was no effect of electrode positioning on fatigue.
- This study suggests that delivering sequential stimulation through multiple electrodes can improve fatigue resistance during recreational, therapeutic and functional NMES use.

ACKNOWLEDGEMENTS

Task Dependent Changes in Motor Neuron Excitability in Humans

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Introduction

- Previously it was believed that motor neurons passively relayed synaptic input to the muscle. Now it is known that motor neurons can generate and amplify current through the activation of persistent inward currents (PICs).

- PICs are mediated by voltage gated ion channels activated below or near recruitment threshold.

- Neuromodulators derived from the brainstem are capable of amplifying PICs up to ten fold. Serotonin and norepinephrine are two prominent neuromodulators.

- It has been demonstrated in animals that the presence of neuromodulators, and therefore intrinsic excitability, changes depending on the task at hand, ranging from low excitability during rapid eye movement sleep, to high excitability during repetitive motor output.

- Trademark characteristics of PICs are higher firing rates at recruitment compared to derecruitment as well as non-linear firing rates.

Purpose

To determine whether the intrinsic excitability of motor neurons changes depending on the task at hand, and if so, assess the range at which this occurs.

Methods

8 participants completed isometric elbow flexion with the elbow flexed about 80 degrees. Motor units were recorded with intramuscular EMG.

$$\Delta F = F recruitment - F derecruitment$$

Conditions:
1. Control
2. Relax
3. Cycle
4. Cold Pressor Test (CPT)

Delta F represents the reduction in synaptic drive needed to maintain unit recruitment. Two motor units are required to calculate Delta F. The lower threshold unit is a measure of synaptic drive to the motor pool. The higher threshold unit is used to indicate the time of recruitment and derecruitment. Delta F is an indirect measurement, thus units must meet two criteria for the pair to be valid.
1. Rate – rate coefficient of determination (R^2) > 0.49
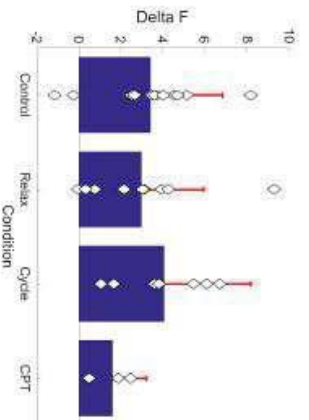2. Time difference between control and test unit onset > 1 second

$$R(t) = R_{max}\left(1 - e^{-(t - t_{on})/\phi}\right) + R_{min}$$

Discharge rates of single units during the ascending phase of a contraction were fit with a saturating exponential function. The sum of squared errors for the linear and exponential fit were compared using an F statistic. If the P-value <0.05, the unit's firing pattern was designated as exponential. An exponential firing pattern suggests the presence of PICs and greater intrinsic excitability.
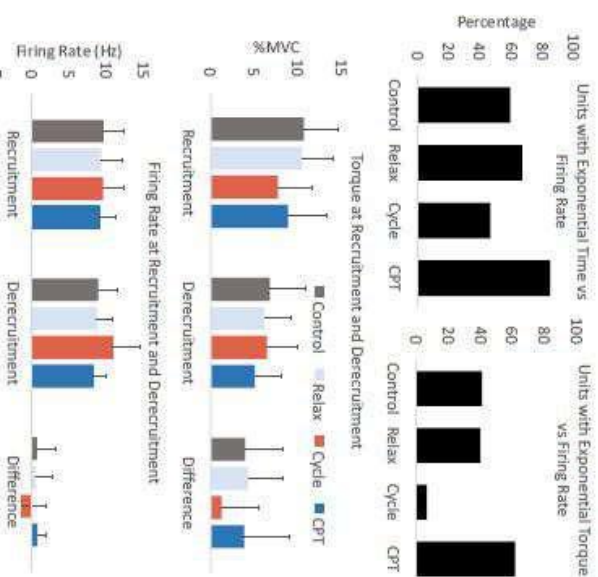
Results

Torque

iEMG

Test Unit
Firing Rate (Hz)

Control Unit
Firing Rate (Hz)

Time (s)

Firing Rate (Hz)

Time (s)

Torque (%MVC)

Motor Unit Pairs

Delta F

Control   Relax   Cycle   CPT
Condition

Single Motor Units

Units with Exponential Time vs Firing Rate
Percentage

Units with Exponential Torque vs Firing Rate
Percentage

Control   Relax   Cycle   CPT

Torque at Recruitment and Derecruitment
%MVC

Recruitment   Derecruitment   Difference

Firing Rate at Recruitment and Derecruitment
Firing Rate (Hz)

Recruitment   Derecruitment   Difference

■ Control ■ Relax ■ Cycle ■ CPT

Conclusion

- We demonstrate preliminary evidence of changes to intrinsic excitability depending on the task at hand, however the ranges are not compatible with animal research. The measurements used may not be precise enough to observe the full range.

- Using the paired motor unit technique, CPT had the lowest intrinsic excitability. The mechanism responsible may be due to a withdrawal reflex that inhibits PICs. However the delta F measurement may not capture true intrinsic excitability because the low threshold unit may not be a linear measure of synaptic drive.

- CPT had the highest percentage of units with exponential firing patterns while Cycle had the lowest. It is probable that contractions produced during Cycle are not smooth enough to generate steady firing rates.

- Further research should be directed towards understanding the effect of other tasks on intrinsic excitability.

Acknowledgements

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Reducing discomfort during neuromuscular electrical stimulation

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INTRODUCTION

Neuromuscular electrical stimulation (NMES) is used to generate contractions of muscles paralyzed by spinal cord injury or stroke. NMES can be delivered over the muscle belly (mNMES) or the nerve trunk (nNMES) and both are used to activate the tibialis anterior (TA) muscle to correct foot drop.

A major limitation of NMES is discomfort, which is due to the activation of nociceptor afferents in the skin or muscle[1]. Discomfort may be reduced using interleaved NMES (iNMES). During iNMES, stimulation pulses are alternated between the muscle site (iNMES$_{(m)}$) and the nerve site (iNMES$_{(n)}$), with different populations of muscle fibers being recruited from each site[2].

We have noticed that to produce the same contraction, stimulation intensity during iNMES is sometimes lower than during mNMES or nNMES alone, and this effect may depend on stimulation frequency.

PURPOSE

Determine the effect of NMES type and frequency on the stimulation intensity (current) required to achieve a given torque, and the corresponding effect on discomfort.

HYPOTHESES

There will be a positive relationship between current and discomfort.

To achieve similar contraction amplitudes, iNMES will require less current and produce less discomfort than mNMES or nNMES alone. Similarly, a given type of NMES delivered at 80 Hz will require less current and produce less discomfort than 20 Hz or 40 Hz.

METHODS

4 healthy volunteers participated. They were seated in the Biodex system with the ankle at approximately 95° and knee at 100° (Fig. 1). mNMES was delivered over TA and nNMES was delivered over the common peroneal (CP) nerve trunk (Fig. 2).
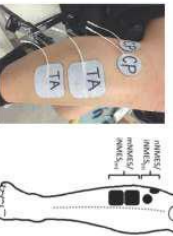

Figure 1. Biodex system set-up.

Figure 2. Electrode placement.

NMES was adjusted to produce ankle dorsiflexion of about 10% of the participant's maximum voluntary contraction (MVC) (Fig. 3).

Figure 3. Experimental protocol. Torque response to 2 second train of NMES (repeated 5 times; 5 second pause; 200 μs pulse width).

Current was measured during mNMES, nNMES and iNMES at frequencies of 20 Hz, 40 Hz and 80 Hz, creating 9 experimental conditions. Participant discomfort was quantified using a visual analogue scale (VAS) after each condition.

Separate 2x3 analysis of variance (ANOVA) tests were used for the muscle site and nerve site to compare current between NMES type at each frequency. A Pearson product-moment correlation (r) was used to quantify the relationship between current and discomfort. VAS Discomfort was compared between NMES type at each frequency using a 3x3 ANOVA test.
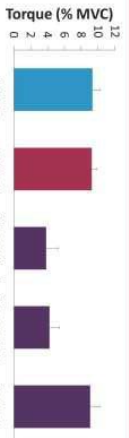
RESULTS

Figure 4. Torque produced at all frequencies during mNMES, nNMES and iNMES was constant at 10% MVC. Torque at individual iNMES sites (iNMES$_{(m)}$ & iNMES$_{(n)}$) was approximately half.
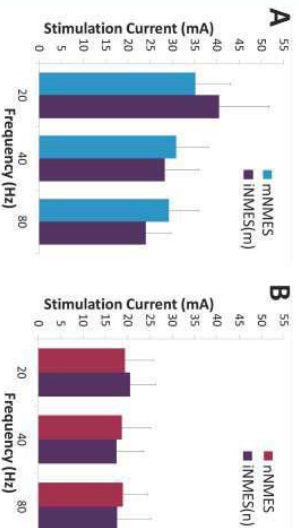

Figure 5. Current required to generate 10% MVC across frequencies at the **(A)** muscle site during mNMES and iNMES and **(B)** nerve site during nNMES and iNMES.
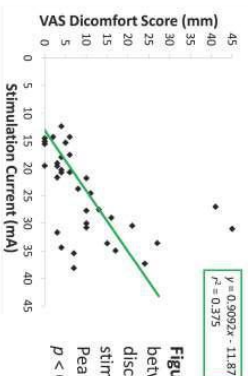

Figure 6. Relationship between VAS discomfort score and stimulation current. Pearson's $r(34) = 0.61$, $p < 0.05$.
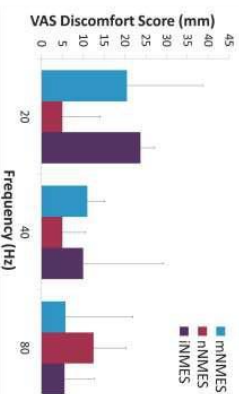
$y = 0.9092x - 11.87$
$r^2 = 0.375$

Figure 7. Average VAS discomfort scores across frequencies during the 3 types of NMES.

CONCLUSIONS

There was a moderate but significant positive correlation between stimulation current and discomfort. There was no significant effect of NMES type or frequency on stimulation current nor discomfort. However, there was a trend for the muscle site to require more current than the nerve site. Additionally, there was a trend for nNMES at 20 Hz and 40 Hz to be the most comfortable. iNMES at 80 Hz may also reduce current and discomfort, but is likely limited by discomfort at the iNMES$_{(m)}$ site. More participants are needed to further this investigation. Manipulating NMES intensity but also type and frequency may reduce discomfort and increase participation in NMES-based rehabilitation.

REFERENCES

1. Delitto et al. (1992) *Physical Therapy* 72(6): 410-421
2. Okuma et al. (2013) *Clinical Neurophysiology* 124(11): 2257-2263

ACKNOWLEDGEMENTS

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Human Neurophysiology Laboratory

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Influence of electrode placement on contraction fatigue during sequential neuromuscular electrical stimulation

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Human Neurophysiology Laboratory
University of Alberta

INTRODUCTION

- Muscle mass, strength and function in individuals with motor impairments can be improved using neuromuscular electrical stimulation (NMES).
- Unnaturally high firing frequencies of muscle fibres during NMES results in rapid contraction fatigue (Fig. 1A).
- During sequential NMES (sNMES), stimulus pulses are rotated between four electrodes over a muscle belly, to recruit different muscle fibres at each electrode and reduce firing frequencies (Fig. 1B).
- Spreading out the electrodes over the muscle could reduce the "overlap" in muscle fibres recruited by each electrode, reducing firing frequency of individual muscle fibres (Fig. 1C and 1D).
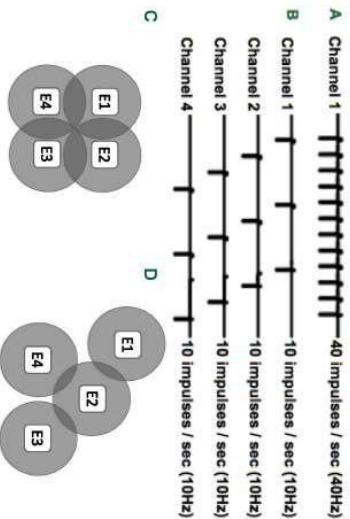
Fig 1. Interleaved sequential NMES pulse timing (adapted from Sayenko et al., Eur J Appl Physiol (2014) 114:793 - 804) **(A)** and **(B)**, muscle fibre recruitment "overlap" with clustered **(C)** and distributed **(D)** electrode placement.

A Channel 1 — 40 impulses / sec (40Hz)

B
Channel 1 — 10 impulses / sec (10Hz)
Channel 2 — 10 impulses / sec (10Hz)
Channel 3 — 10 impulses / sec (10Hz)
Channel 4 — 10 impulses / sec (10Hz)

C E4 E1 / E3 E2

D E1 E2 E3 E4

OBJECTIVE & HYPOTHESIS

Objective: Examine the effect of electrode placement, clustered or distributed over the quadriceps muscle, on contraction fatigue during sNMES.

Hypothesis: Contraction fatigue will be less due to reduced "overlap" in muscle fibre recruitment and firing frequency with distributed electrode placement compared to clustered electrode placement.

METHODS

sNMES was applied over the quadriceps in 8 participants (4 females and 4 males aged 30.4 ± 11.9 years).

Fig 2. Clustered **(A)** and distributed **(B)** electrode placements. **(C)** Biodex apparatus used to measure isometric knee extension torque.

METHODS

Maximum voluntary contraction (MVC) torque was measured before and after "fatigue protocols" delivered using clustered and distributed electrode placements.

Fatigue protocol:
sNMES was delivered at 40Hz with a 0.3 sec "on" and 0.7 sec "off" duty-cycle producing 170 contractions over 3 min

sNMES was delivered to produce an initial contraction of ~15% MVC.

Data were averaged over 5 successive contractions to form 34 bins.
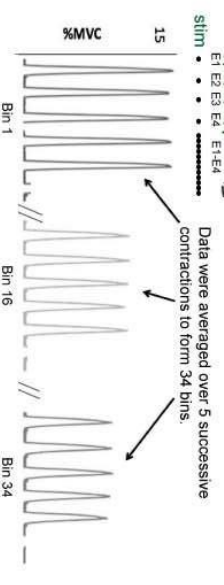
Outcome measures:
Peak torque decline over the fatigue protocols and change in MVC peak torque. All data are presented as the mean ± one standard deviation.

Analyses:
% Δ MVC = $\frac{\text{Post MVC (Nm)} - \text{Pre MVC (Nm)}}{\text{Pre MVC (Nm)}} \times 100$ → 2 × 3 ANOVA with repeated measures

Fatigue Index = $\frac{\text{Peak torque of last binned contractions}}{\text{Peak torque of first binned contractions}} \times 100$ → Paired samples t-test

Peak torque of first and last binned contractions during fatigue protocol → 2x2 ANOVA with repeated measures
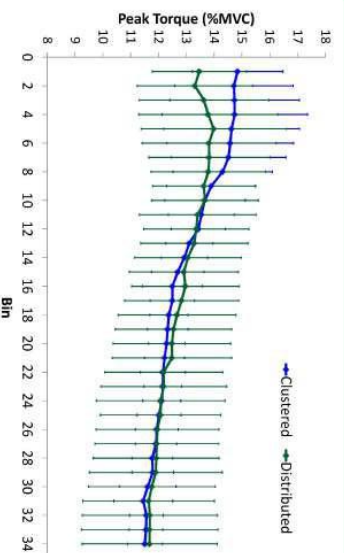
RESULTS

Fig 3. Group (n=8) peak torque during fatigue protocols delivered using clustered and distributed electrode placement. Each point represents data averaged over 5 consecutive contractions to form a bin.
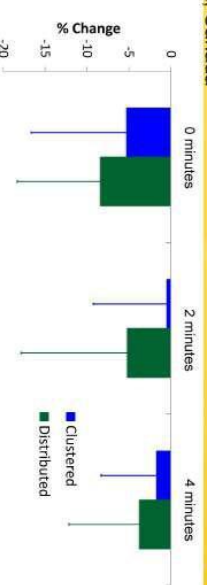
Peak Torque (%MVC) vs Bin — Clustered / Distributed

Fig 4. Group (n=8) change in MVC at 0, 2 and 4 minutes post-fatigue protocol with clustered and distributed electrode placement. — Clustered / Distributed
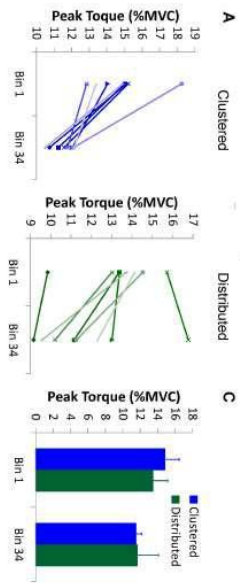
Fig 5. Peak torque of the first and last 5 consecutive contractions during the fatigue protocol for individual subjects with clustered **(A)** and distributed **(B)** electrode placement. Group peak torque of the first and last 5 consecutive contractions during the fatigue protocol (n=8) **(C)**.
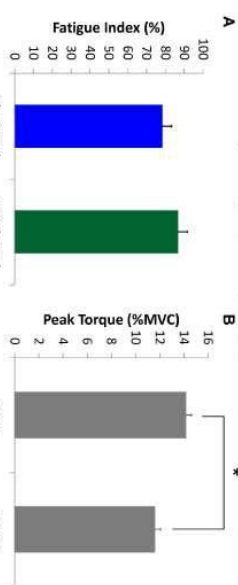
CONCLUSION

Fig 6. Effect of electrode placement on fatigue index (n=8) **(A)** Pooled peak torque from the first and last 5 consecutive contractions during fatigue protocol (n=8) showing a main effect of time **(B)**

- There was no significant difference in contraction fatigue between conditions, as measured by fatigue index, change in peak torque during the fatigue protocol and percent change in MVC.
- Torque declined approximately 17.5% during the fatigue protocols, regardless of electrode placement, thus fatigue was induced by the protocol (p < 0.001).
- MVC peak torque measured immediately after the fatigue protocol showed a decline of approximately 6.8% similarly across conditions.
- Electrode positioning does not have a significant effect on fatigue.
- Clustered electrode placement is more straightforward making it easier to implement in a clinical setting.

ACKNOWLEDGEMENTS

Theory and Measurement of Nerve Excitability

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[1]Faculty of Physical Education & Recreation, University of Alberta [2]Biomedical Engineering Department, Universidad Iberoamericana, [3]Neuroscience and Mental Health Institute, University of Alberta

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Intro to Nerve Excitability

Measuring Nerve Health:

- **Non-invasive *in vivo***
- Application of conditioning/test stimuli at different amplitudes, pulse widths, and delays to indirectly measure axonal properties and function
- Differential distribution of ion channels in axons allows for the possibility of specific excitability measures for each compartment
- Discrete measures from a set of tests are sensitive to ion channel biophysics, number and location

What is Threshold?

Threshold in Nerve Excitability

- **Amount of current needed to meet a target CMAP response**
- Expressed as a % of $CMAP_{max}$, determined by Stimulus-Response Curve
- Used as a target response to be met during excitability measures (Conditioning pulse followed by a test pulse attempting to reach the set target response – **40% $CMAP_{max}$**)

Traditional Definition

- Amount of current needed to depolarize from resting membrane potential to trigger an action potential
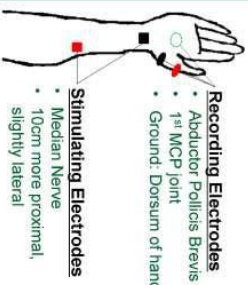
Methods

- Pre-screening for Neuropathies, and drugs known to affect peripheral nerves
- Documents and ethics forms
- Skin preparation, electrode placement, temperature monitoring
- Running TROND protocol (data acquisition)
- Data Collected on Median and Common Peroneal Nerves
- Data analysis with QtracP, and MatLab
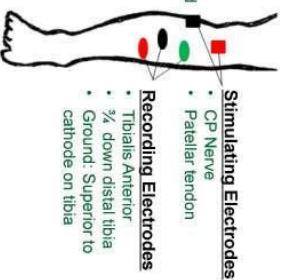
Equipment

- **Digitimer DS5 stimulator**, deliver square wave pulses, widths 0.2-200ms, input voltage ±10V, output current ±50mA
- **Digitimer D440 amplifier**
- **Hum Bug filter**, real time signal processing removes 50/60Hz frequencies
- **National Instruments USB-6251** BNC data acquisition board
- **Digitimer QtracW Software** data collection, and conducting tests
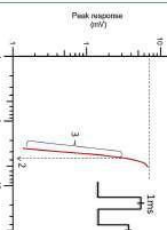
Electrode Placement

Median Nerve

Stimulating Electrodes
- Median Nerve
- 10cm more proximal, slightly lateral

Recording Electrodes
- Abductor Pollicis Brevis
- 1st MCP joint
- Ground: Dorsum of hand

Common Peroneal Nerve

Stimulating Electrodes
- CP Nerve
- Patellar tendon

Recording Electrodes
- Tibialis Anterior
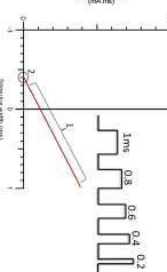- ¼ down distal tibia
- Ground: Superior to cathode on tibia

Excitability & Discrete Measures

Stimulus Response

1. Maximal response (mV)
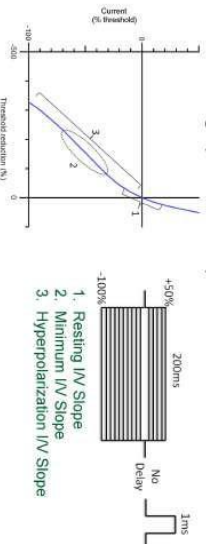2. Stimulus (mA) for 50% max response
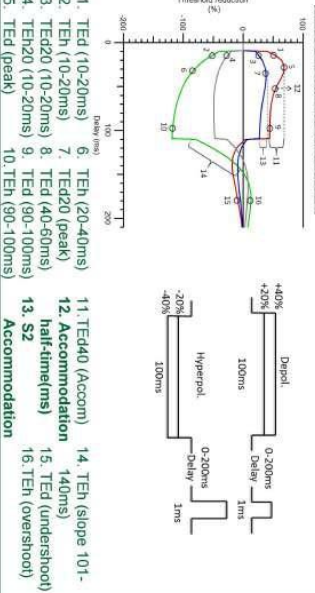3. Stimulus Response Slope

Recovery Cycle

1. Relative Refractory Period (ms)
2. Superexcitability (%)
3. **Subexcitability (%)**
4. Refractoriness at 2.5ms (%)
5. Superexcitability at 5ms (%)
6. Superexcitability at 7ms (%)

### Current Voltage (Threshold I/V)

1. Resting I/V Slope
2. Minimum I/V Slope
3. Hyperpolarization I/V Slope

Threshold Electrotonus

1. TEd (10-20ms)
2. TEh (10-20ms)
3. TEd20 (10-20ms)
4. TEh20 (10-20ms)
5. TEd (peak)
6. TEh (20-40ms)
7. TEd20 (peak)
8. TEd (40-60ms)
9. TEd (90-100ms)
10. TEh (90-100ms)
11. TED40 (Accom)
12. **Accommodation half-time(ms)**
13. **S2 Accommodation**
14. TEh (slope 101-140ms)
15. TEd (undershoot)
16. TEh (overshoot)

Charge Duration

1. Rheobase (mA)
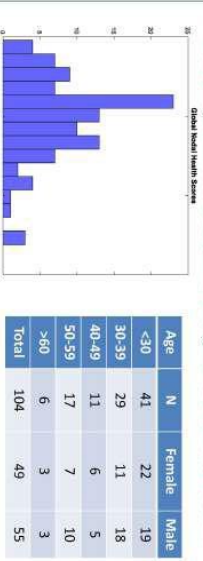2. Strength Duration Time Constant (ms)

Nodal Health
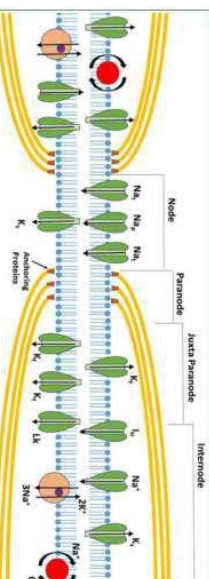
Can it be Measured?

- Node has high concentrations of Na^+ Transient ($Na_v1.6$) and Persistent ion channels, and slow K^+ ion channels ($K_v7.2$)
- Took discrete measures known to indirectly measure these ion channels, checked for normal distribution, 6/7 measures passed
- Normalized scores from discrete measure can be added to provide a measure of nodal health

Results

Nodal Health

- Data collected from 104 participants (55 male), 39% <30 yrs.
- 104 Median Nerve, 92 Common Peroneal Nerve, 82 Repeated Measures
- Female nodal health score range: -5.2852 to 7.0662 (more symmetric dist.)
- Male nodal health score range: -3.7528 to 8.3732 (slightly right skewed)
- Nodal health does not seem to be related to age (current data limitations)
- High nodal health scores does not guarantee high values for all measures of nodal health or that other discrete measures will be high
- More analysis needed to determine strength of each discrete measure

Age	N	Female	Male
<30	41	22	19
30-39	29	11	18
40-49	11	6	5
50-59	17	7	10
>60	6	3	3
Total	104	49	55

Outliers

	Stim (mA) 50% max response	SDTC (ms)	Rheobase (mA)	Subexcitab-ility(%)	Accommo-dation(%)	Accommod-ation half-time (ms)
JA18N	7.272	0.473	4.956	21.3	28	43.23
RE27Y	4.168	0.543	2.681	30.44	38.44	38.58
AR19E	11.69	0.382	7.691	15.98	22.53	36.33
VA03N	9.203	0.39	6.095	19.5	26.71	35.69
Median	3.904	0.424	2.66	15.74	22.14	39.5
Mean		0.4228	16.02	22.49	40.39	
SD	1.485	0.08184	1.501	5.467	3.64	5.147

References:
Kiernan, M. (n.d.). [Diagram of a myelinated axon illustrating ion channels, pumps, and exchangers]. Retrieved March 6, 2017, from https://www.researchgate.net

Schott, G. D. (2013). Revealing the invisible: the paradox of picturing a phantom limb. *Brain*, 137(3), 960-969. doi:10.1093/brain/awt244

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FACULTY OF PHYSICAL EDUCATION AND RECREATION

Development of Professional Identity in Pharmacy Students: A National Survey

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University of Alberta, Edmonton

INTRODUCTION

- Professional identity is defined as being able to "think, act, and feel" like a pharmacist.
- The primary identity within the AFPC outcomes is the care provider identity. However, there are many unique identities of pharmacists, which leads to role confusion and lack of clear professional direction. This contributes to dissonance within students professional aspirations and what they have learned with their experience in practices.
- Professional identity formation is a complex and dynamic process and has not been well studied in pharmacy students.

OBJECTIVE

Describe which elements of curricular and non-curricular activities in pharmacy student life may contribute to professional identity formation

METHODS

DESIGN: Anonymous cross-sectional survey

PARTICIPANTS: Email invites were sent by Canadian Association of Pharmacy Students and Interns (CAPSI) representatives at all 10 Canadian pharmacy schools

DATA COLLECTION: At the start of the survey, two short answer open-ended questions were posed:
1. What does "professionalism" mean to you?
2. What does the term "professional identity" mean to you?
- Students were asked to indicate if they had heard of professional identity as defined and to rank the importance of its development
- Students were also asked to share how supported they felt the development of their professional identities and to indicate which experiences they felt had or could better influenced their development.

ANALYSIS:
- Responses were coded using either a deductive or an inductive approach, wherein a systematic three stage qualitative analysis was used to create codes.
- Stage 1 involved paraphrasing the interviewee's responses into meaningful segments or concepts. Stage 2 required the reduction of these major concepts into 2-5 word statements. Finally, these statements were coded with 1-2 words that captured the essence of the ideas. These codes were then organized into emerging themes for reporting purposes.

RESULTS

Table 1: Demographic characteristics of pharmacy students (n=172)

Characteristic	n (%)
School (n =149)	
University of British Columbia	4 (2.7)
University of Alberta	67 (45)
University of Saskatchewan	19 (12.8)
University of Manitoba	14 (9.4)
University of Waterloo	7 (4.7)
University of Toronto	15 (10.1)
Université de Montréal	4 (2.7)
Université Laval	11 (7.4)
Dalhousie University	4 (2.7)
Memorial University of Newfoundland	4(2.7)
Year of study (n =149)	
Year 1	42 (28.2)
Year 2	41 (27.5)
Year 3	38 (25.5)
Year 4	28 (18.8)
Age category prior to starting pharmacy school (n =151)	
19-24	140 (92.7)
25-30	9 (6)
31-40	2 (1.3)
Highest level of postsecondary completion (n =151)	
Partial competition of undergraduate degree	90 (59.6)
Undergraduate degree	57 (37.7)
Graduate degree	4 (2.7)

Figure 1: Definition of professionalism

Basic role of the pharmacist
Responsibility and accountability
Professional stewardship
Honesty and integrity
Professional presence
Dedication and commitment to excellence
Respect for others
Altruism

Students responses fell into two main categories: traditional view of professionalism or the expanded view of professionalism. The top three common attributes were professional presence, respect for others and honesty and integrity.

Figure 2: Definition of professional identity

Dynamic **Competence**
External perception
Professional Identity
Designation
Internal Set of skills

Students responses fell into two main categories: traditional professionalism definitions (external perception, set of skills, designation, competence) or a more internalized view of professional identity (dynamic, internal, professional identity)

Figure 3: Opportunities for faculty and student associations
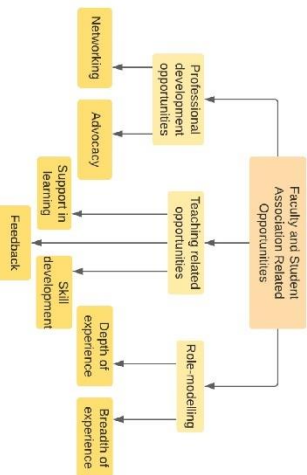
DISCUSSION

- Many students equate being nice with being professional. Some students believe professionalism is acting professional where some believe it is being professional.
- Students recognize that teaching related opportunities, professional development and role-modelling play a key role in developing professional identities.

CONCLUSIONS

- Most pharmacy students struggle to define professional identity and distinguish it from professionalism.
- In order to nurture professional identity development, the curriculum, pharmacy faculty, and student associations must intentionally design opportunities for student growth.

ACKNOWLEDGEMENTS

*References available upon request

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HIV Treatment Outcomes in a Conflict Setting: Results from a Five-Year Programme in the Central African Republic

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1) Médecins Sans Frontières, Bangui, Central African Republic
2) Médecins Sans Frontières, Berlin, Germany
3) Médecins Sans Frontières, London, United Kingdom

Introduction

The Central African Republic (CAR), one of the world's poorest countries, has low access to anti-retroviral therapy (ART; 13.8%) despite an estimated 120,000 people living with HIV and 11,000 AIDS related deaths annually. The Central African Republic faces a number of challenges in healthcare provision including instability and civil conflict along with a lack of infrastructure outside of the capital Bangui. Consequently, the mortality rate per 1000 people living with HIV is the highest in the world (Granich *et al.* PLoS ONE 2015).

We report on treatment outcomes from a HIV patient cohort on a program of ART provision in a rural setting in CAR for >5 years. The HIV program in Zemio, Haut-Mboumou prefecture was set up initially to provide support to an influx of Congolese refugees and internally displaced people forced to leave their homes due to repeated attacks by the Lord's Resistance Army from 2008-10.

Figure 1. Regions of Central African Republic. Black box indicates the study site; Zemio Town and the surrounding Haut-Mbomou and Mbomou prefectures.

Objectives

- To evaluate the impact of the ART program through:
  1) mortality rate
  2) CD4 T-cell count recovery

- In addition we identified risk factors for patient mortality

Methods

We analysed data collected from the program between October 2011 and April 2017. The program offered ART to individuals with CD4 counts <500 cells/mm3, first-line therapy was selected according to WHO recommendations at the time of entry.

Covariates were taken at baseline (age, height, weight, sex, CD4 T-cell count, viral load, clinical staging of opportunistic infections) and counts of CD4 cells and viral load were updated every 6 months. Mortality during the study was reported directly if patients died in hospital or by health workers in the community. The survival rate was estimated using Cox's proportional hazards model.
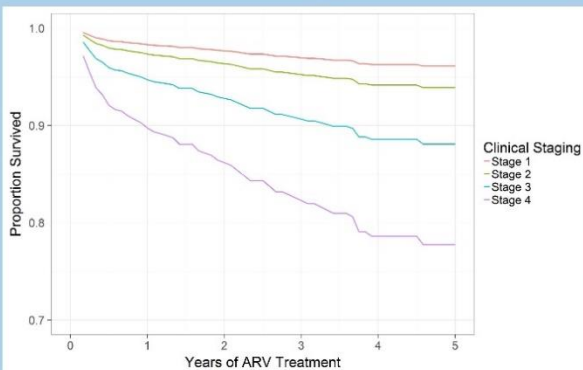
Figure 2. Survival Curves estimated from Cox's Proportional Hazard Model. Patients are stratified by clinical staging of opportunistic infections (OIs) at baseline according to WHO guidelines. Patients starting ART with clinical stage OIs 3 and 4 had a significantly greater risk of death (hazard ratio) than patients in stage 1 (p< 0.05), when sex and age were included as covariates. Note the y-axis is truncated at 0.7.
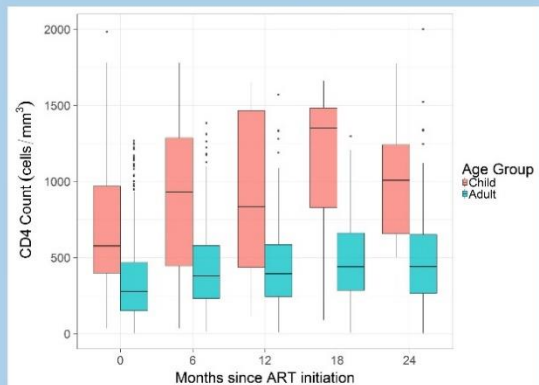
Figure 3. Immunological recovery of CD4 T-Cells following treatment with ART. Data are shown at baseline (n= 1027) and 6 (n=350), 12 (n=256), 18 (n=181) and 24 (n=203) months subset by age groups; children (≤16 years) and adults. Numbers of CD4 cells increased significantly compared to baseline at 12, 18 and 24 months (p < 0.05), as estimated through a generalised linear model that included an interaction term with age.

Results

In total 1504 HIV positive individuals were treated with ART. This gave a total of 2429 patient years and the median time in the cohort was 12 months. A total of 119 deaths were reported over the period, of which 62 were in the first 6 months of ART provision (Table 1). The proportion of patients that survived after 12 months was 0.952 (95% CI; 0.939, 0.965), though the severity of opportunistic infections at baseline contributed significantly to heterogeneity in survival (Figure 2). Men had double the risk of mortality compared with women (p<0.01). The median CD4 count at baseline among adults was 228 cells/mm3, and this rose significantly after 12 months of treatment to 395 cells/mm3 (Figure 3).

Period	Baseline	6 Months	12 Months	18 Months	24 Months
At Risk	1504	1028	803	628	504
Deaths over period	NA	62	14	8	8

Table 1. Number of patients at risk and number of deaths reported over the first 24 months of ART.

Conclusion

Despite the challenges of operating in a low-resource, conflict setting the HIV program in Zemio has delivered positive outcomes for patients, alongside competing priorities. The survival rate after 12 months is equal to or greater than values reported from studies in more stable African settings (Lawn *et al.* AIDS 2008). The rate of CD4 cell recovery suggests that patients are adhering to therapy and that the health promotional messages of the hospital have been understood and accepted by patients. We propose that it is possible to provide longevity and improve the quality of life of HIV positive patients even in the poorest countries, and that improving access to ART should be a priority for African governments and donors.

Antimicrobial resistance in low-resource settings: a point prevalence survey in the MSF hospital "Centre de Référence pour les Urgences Obstétricales", Port au Prince, Haiti.

Katerina Chaintarli[1,2,3], Bregeneve Dabord Beauzile[3], Rodnie Senat-Delva[3], Chiara Martino[4], Marine Berthet[3], Joost Hopmann[4,5], Annick Lenglet[4]

[1]European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Solna, Sweden, [2]Health Protection Surveillance Centre, Dublin, Ireland, [3]Médecins Sans Frontières Operational Centre Amsterdam, Port au Prince, Haiti, [4]Médecins Sans Frontières, Operational Centre Amsterdam, Amsterdam, The Netherlands, [5]Radboud University Medical Center, Nijmegen, The Netherlands

Introduction

- Centre de Référence pour les Urgences Obstétricales (CRUO): obstetric and neonatal emergency care hospital in Port au Prince, Haiti;
- In 2014 an outbreak of sepsis from extended-spectrum β-lactamase (ESBL) producing *Klebsiella pneumoniae* was observed in the neonatal intensive care unit;
- Antimicrobial surveillance, infrastructure and infection control and prevention measures (IPC) were improved but nosocomial transmission of Gram-negative bacteria continued in 2015/2016;
- Antibiotics used:
  - Infants: gentamycin (1st line), ceftazidime-amikacin (2nd line), imipenem (3rd line);
  - Women: gentamycin (1st line), amoxicillin/clavulanic acid (2nd line)
- **Objectives of the study were to estimate**:
  - prevalence of colonisation with Gram-negative bacteria;
  - prevalence of ESBL positive isolates;
  - prevalence of resistance to antibiotics in bacterial isolates.

Figure 1: Floor plan of wards sampled for the current study in CRUO - Haiti, July 2016.
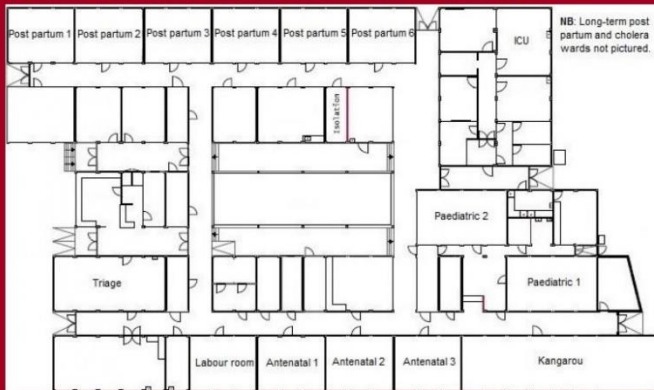
Table 1: Prevalence of bacteria by admission room for infants, MSF CRUO Haiti, July 2016.

Admission Room	N	K.pneumoniae (%)	K.oxytoca (%)	E.coli (%)	E. cloacae (%)
Kangarou	10	2 (20.0)	2 (20.0)	7 (70.0)	0 (0)
Post-partum	10	4 (40.0)	0 (0)	5 (50.0)	1 (10.0)
Labour room	2	0 (0)	0 (0)	1 (50.0)	0 (0)
Long-term post-partum	8	3 (37.5)	0 (0)	6 (75.0)	0 (0)
Isolation	6	3 (50.0)	0 (0)	3 (50.0)	0 (0)
Paediatric 1	14	3 (21.4)	2 (14.3)	3 (21.4)	0 (0)
Paediatric 2	14	2 (14.3)	0 (0)	6 (42.9)	0 (0)
Total	64	17 (26.6)	4 (6.3)	31 (48.4)	1 (1.6)

Figure 2: Proportion of ESBL positive isolates by admission room among women, CRUO-Haiti, 2016
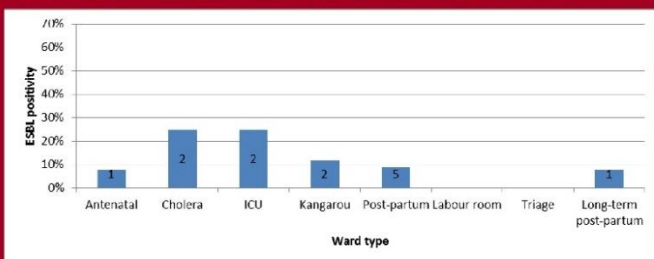
Figure 3: Proportion of ESBL positive isolates by admission room among infants, CRUO-Haiti, 2016
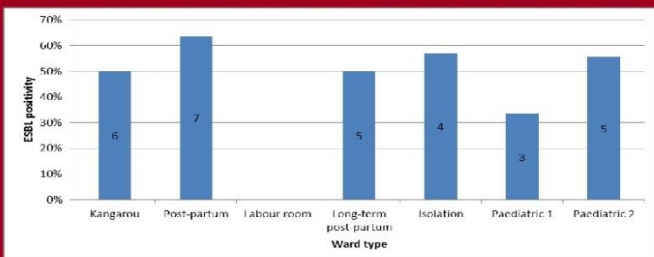
Methods

- **Study design**: Point prevalence study;
- Rectal swabs collected from all admitted neonates, women in triage and admitted women in CRUO between 11th and 22nd July 2016;
- Data collection form: demographics, admission room, date of admission and antibiotic treatment history;
- All patients and parents/caretakers provided informed verbal consent for participation;
- Antibiograms and ESBL positivity determined in the local lab;
- Rectal swabs were cultured and identification and susceptibility testing was performed using the Vitek2 GN;
- **Statistical analysis**: prevalence calculations were conducted in STATA 14.1.

Results

- We collected swabs from 112 women and 64 infants (99% response) across all wards (Figure 1);
- Twenty seven percent of neonates (17/64) were colonised with *Klebsiella pneumoniae* (Table 1);
- Colonisation with *K. pneumoniae* was highest among neonates in isolation (50%; 3/6) (Table 1);
- Of all *K. pneumonia* isolates, 27% (4/15) among women and 59% (10/17) among neonates were ESBL-positive (all resistant to first line antibiotics);
- Among women, the median prevalence of ESBL-positive bacteria was 8.3% (Figure 2);
- Among infants, prevalence of ESBL-positive bacteria was higher than women and the median was 50% (Figure 3);
- No ESBL-positive isolates were identified in the labour room or triage at admission (Figures 2 & 3);
- Resistance of *K. pneumonia* isolates to second-line antibiotics was 20% (3/15) for women and 6% (1/17) for neonates (Figure 4);
- One *Klebsiella sp.* isolate (ESBL positive) from a neonate was resistant for carbapenems (third-line antibiotics).

Figure 4: Antimicrobial resistant patterns for *Klebsiella pneumoniae* isolates from women (a) and infants (b), CRUO-Haiti, 2016
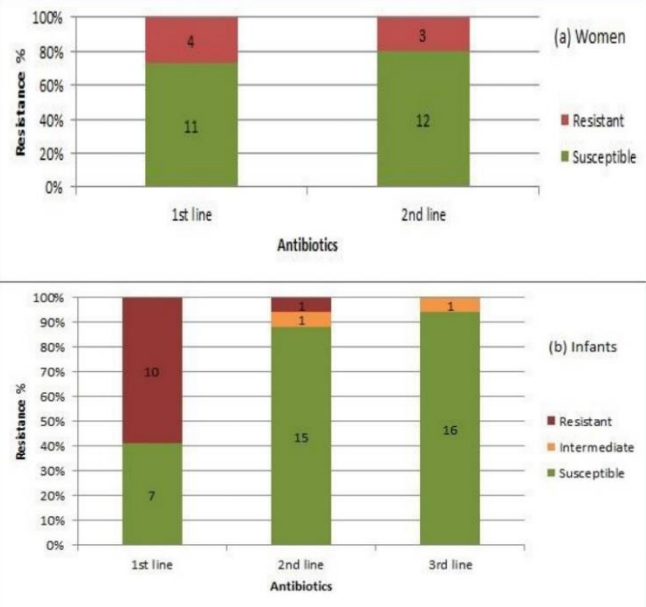
Conclusions

- Point prevalence survey provided new and clear insights in the epidemiology of Multidrug resistant microorganisms in CRUO;
- Highest colonisation prevalence and ESBL positivity in wards where patients stay longer or end up after a long stay in the hospital;
- Higher ESBL colonisation in infants in comparison to women;
- Absence of ESBL positive bacteria in Triage suggests colonisation mainly occurs during hospitalisation;
- High resistance rates to first line treatment in infants;
- First carbapenase resistant Klebsiella pneumonia ESBL isolated;
- Regular evaluations of the appropriateness of existing antibiotic treatment protocols and strengthening infection prevention measures are necessary.

COMPARING PHARMACOLOGY EDUCATION

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INTRODUCTION

Objective: To investigate and highlight methods of teaching that were most effective to medical students.

Knowledge in pharmacology is important for medical students in both clerkships and future practice. However, methods of teaching pharmacology are widely variable among medical schools. We aim to survey medical students and identify the most effective methods of teaching.

METHODS

An online survey was developed and delivered to second year medical students or equivalent pre-clinical year. The survey focused on four main themes:

1) Mode of teaching pharmacology at their school.
2) Satisfaction with their pharmacology program.
3) Strength and weakness of their pharmacology education.
4) Student's background education prior to medical training.
5) Their confidence in safely prescribing medications in residencies.

Responses were collected from medical schools in Canada, Australia, and the United Kingdom. We then used students' perceived level of their own pharmacology education as outcome. Factors of methods of teachings were compared with outcomes to find associated factors using Spearman's coefficients and p values of <0.05 were used to determine significant results. In addition, the most recommended methods of teaching are tallied and identified.

RESULTS

Table 1: Correlation between Confidence in Prescribing and Characteristics of Pharmacology Education

Characteristics of Pharmacology Education		Confidence in prescribing				Spearman coefficient (rho)	P-value
		1	2	3	4		
Adequate amount of time spent	1	6	3	0	0	0.406	0.000
	2	10	47	7	1		
	3	4	18	16	0		
	4	0	2	5	1		
Faculty recommended apps	Yes	1	8	5	1	-0.182	0.050
	No	19	62	20	0		
Self-directed learning	Yes	3	24	15	0	-0.276	0.003
	No	17	46	10	1		
Quizzes	Yes	2	13	9	0	-0.193	0.038
	No	18	57	16	1		
No end of term exams	Yes	0	1	3	0	-0.201	0.023
	No	20	69	22	1		

- There was a positive correlation between respondents' feeling there was an adequate amount of time spent on pharmacology education (rho=0.406, p=0.000), and confidence in prescribing medications.
- Self-directed learning (rho=-0.276, p=0.003), having quizzes (rho=-0.193, p=0.038), and having no end of term exams (rho=-0.201, p=0.023) were negatively correlated with students' subjective views on their confidence in prescribing medications.

Table 2: Correlation between Current Pharmacology Knowledge and Characteristic of Pharmacology Education

Characteristic of Pharmacology Education		Current Knowledge				Spearman coefficient (rho)	P-value
		1	2	3	4		
Adequate amount of time spent	1	1	6	1	1	-.370	.000
	2	0	19	37	9		
	3	0	3	24	11		
	4	0	0	3	1		
Faculty recommended apps	Yes	1	8	5	2	-.199	.032
	No	0	20	60	20		

- Feeling as though an adequate amount of time was spent on pharmacology education (rho=0.370, p=0.000) and having faculty recommended apps (rho=0.199, p=0.032) were positively correlated to current knowledge.

Table 3: Recommended Methods of Pharmacology Education by Respondents

Methods	Number of people /116	Percentage (%)
Pharmacology lecture integrated into each block	19	16.4
Single block of pharmacology	27	23.3
Pharmacology handbook availability	76	65.5
Virtual cases	37	31.9
Small group discussions	34	29.3
Research projects	6	5.2
Self-directed learning	9	7.8
Clinical exposures	48	41.4
Quizzes	34	29.3
End of term exams	6	5.2

CONCLUSION

- Factors correlated with positive outcome:
  1) Adequate time in pharmacology education (suggested to be 100 hours/year on average).
  2) Faculty recommended smart phone apps.
  3) Prior pharmacology knowledge.

- Factors correlated with negative outcome:
  1) Self directed learning (including problem-based learning)
  2) Regular quizzes.
  3) Lack of term exams.

- Top recommendations:
  1) Providing pharmacology handbook.
  2) Increase clinical exposures
  3) Virtual cases.

FUTURE DIRECTIONS

- Use of objective measurements as outcome.
- Implementation of recommendations to allow assessments.

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USciences
University of the Sciences

Clinical Trial Summaries: Readability to Effectively Inform Patients

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Where healthcare and science converge.

Objectives

- To increase awareness regarding effective communication of clinical trial summaries and how it relates to patient participation and compliance in clinical trials
- To suggest the application of readability formulas to assure public understanding of disseminated reports

Introduction

Public disclosure of clinical trial summaries by the research community is steadily increasing in frequency as transparency policies take effect around the globe[1]; however, these study reports are still not often fully understood by patients and the public.

Current efforts to translate clinical trial summaries from technical to common language are effective when the target audience is members of the scientific or medical community.

Communicating the same information to patients still poses a challenge since governing bodies enacting transparency policies have not fully explored the comprehension of clinical trial data by the public. The average grade level reading ability for general public in the United States is 8th grade.[2]

Current efforts in the United States to publish clinical trial summaries for public dissemination includes the following:
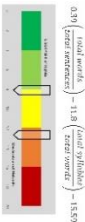
- US National Library of Medicine (clinicaltrials.gov) is a web-based interface that publishes clinical studies and their results for everyone from patients to researchers.[3]
- The Center for Information and Study on Clinical Research (CISCRP) is a non-profit organization that focuses on education about clinical trials and works to improve patient communication.[4]

Methods

To establish a baseline understanding of the output of the available readability algorithms, the readability of The Declaration of Helsinki and The CISCRP Participant Bill of Rights were analyzed using an online tool (https://readable.io/) which analyzes text with 5 different established algorithms.[5]

- **Flesch-Kincaid Grade Level**
  - Rates text on a U.S. school grade level. For most documents, aim for a score of approximately 7.0 to 8.0.

$$0.39 \left(\frac{total\ words}{total\ sentences} \right) + 11.8 \left(\frac{total\ syllables}{total\ words} \right) - 15.59$$

- **Gunning Fox Index**
  - An interpretation is that the text can be understood by someone who left full-time education at a later age than the index.

$$0.4 \left[\left(\frac{total\ words}{total\ sentences} \right) + 100 \left(\frac{complex\ words}{total\ words} \right) \right]$$
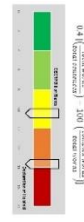
- **Coleman-Liau Index**
  - Estimates the years of formal education the reader requires to understand the text on the first reading.

$$4.71 \left(\frac{total\ characters}{total\ words} \right) + 0.5 \left(\frac{total\ sentences}{total\ words} \right) - 12.43$$
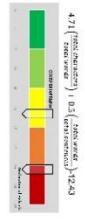
- **SMOG Index**
  - Estimates the years of education needed to understand a piece of writing. Simple Measure Of Gobbledygook.

$$3 + \sqrt{words\ with\ 3\ or\ more\ syllables \times 30 \over total\ sentences}$$
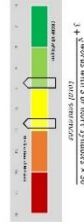
- **Automated Readability**
  - Approximate representation of the US grade level needed to understand a piece of text comprehend the text.
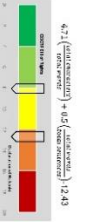
To assess readability of clinical trial summaries, four clinical trials were selected based on their availability on the CISCRP website. The trial summaries were retrieved from the clinicaltrial.gov database as well as from CISCRP. The 5 scoring algorithms were applied to each version of the clinical trials with https://readable.io.

NCT00611026 fesoterodine in overactive bladder

NCT00623233 gemcitabine plus bevacizumab in breast cancer

NCT01016680 duloxetine versus placebo in osteoarthritis

NCT01057693 pregabalin for diabetic peripheral neuropathy

Results

NCT00611026

Grade Level chart — CISCRP FESTOSTERONE / CLINTRIAL FESTOSTERONE
(Flesch Kincaid Grade Level, Gunning Fog Score, Coleman Liau Index, SMOG Index, Automated Readability Index)

NCT01016680

Grade Level chart — CISCRP DULOXILINE / CLINTRIAL DULOXILINE
(Flesch Kincaid Grade Level, Gunning Fog Score, Coleman Liau Index, SMOG Index, Automated Readability Index)

NCT01057693

Grade Level chart — CISCRP PREGABALIN / CLINTRIAL PREGABALIN
(Flesch Kincaid Grade Level, Gunning Fog Score, Coleman Liau Index, SMOG Index, Automated Readability Index)

NCT00623233

Grade Level chart — CISCRP GEN BEVACIZUMAB / CLINTRIAL BEVACIZUMAB
(Flesch Kincaid Grade Level, Gunning Fog Score, Coleman Liau Index, SMOG Index, Automated Readability Index)

Conclusions

Clinical trial summaries published by the clinicaltrials.gov are more difficult to read for the general population when compared to the same trials published by CISCRP. Regular application of readability formulas as a part of the writing process ensures appropriate comprehension levels for public dissemination.

Grade level 16

Silicone, when injected into areas with many blood vessels such as the buttocks, can travel to other parts of the body and block blood vessels in the lungs, heart or brain. This can result in permanent damage to those tissues and lead to stroke or death. Surgery to remove large-scale injectable silicone may present additional risks and serious complications, and may not entirely rid the body of the silicone. Multiple medical and surgical interventions are sometimes needed to treat symptoms years after initial injection; even then, patients may continue to experience ongoing pain, infection, and scarring and permanent disfigurement requiring ongoing treatment.

Grade level 11

When silicone enters your body, it can spread and move around. This effect may make it difficult to remove if there are any serious side effects. Silicone, injected into your buttocks can travel to your lungs, heart or your brain causing damage leading to stroke or death. Many surgeries are often necessary to remove silicone from your body. After the silicone removal surgeries, you still may experience pain, scarring and permanent deformities.

Patient comprehension may increase participation and study compliance as the patients are armed with the knowledge of how their involvement helps.

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Sky Watson: Scientist – Roche Tissue Diagnostics

Evaluation of Canadian Pharmacists' Knowledge and Comfort in the Management of Epilepsy and Antiepileptic Drugs

UNIVERSITY OF ALBERTA
FACULTY OF PHARMACY AND
PHARMACEUTICAL SCIENCES

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INTRODUCTION

- Epilepsy is the most common purely neurological disorder affecting more than 50 million people worldwide and seizures can have a significant impact on quality of life.
- Antiepileptic drugs (AEDs) remain the mainstay of epilepsy management but one of the greatest challenges comes with optimizing the balance between seizure control and side effects of therapy.
- Pharmacists' involvement in the care of patients with chronic conditions can make a significant difference to patient outcomes[1] and pharmacists have the potential to play an integral role in the management of epilepsy and AEDs.
- While some international studies have shown a gap in knowledge in the management of epilepsy and the need for support tools[2,3], little is known about Canadian pharmacists' knowledge and comfort in the management of epilepsy and AEDs.

OBJECTIVES

To characterize Canadian Pharmacists' knowledge and comfort in managing epilepsy and antiepileptic drugs and conduct a needs assessment to aid in the future development of pharmacy-specific epilepsy educational support tools.

METHODS

Ethics: The study was approved by the Health Research Ethics Board of the University of Alberta.

Design: Anonymous cross-sectional electronic survey.

Population: A secure link to the survey hosted on REDCap was distributed to licensed pharmacists in Canada through professional organizations and social media outlets.

Data Collection:
- Survey designed and developed through evidence-based guidelines and designed to target knowledge most relevant to pharmacists.
- Consisted of multiple-choice questions with four sections including demographics, knowledge, comfort and needs assessment around epilepsy management and AEDs.

Data Analysis
- Descriptive statistics were used to summarize demographic, comfort, knowledge and needs data.
- Predictors of knowledge scores greater than 50% were determined using multivariate logistic regression.
- Data analysis was conducted using Microsoft Excel and STATA software v.15.1.

RESULTS

Table 1: Overview of Key Demographics and Practice-Related Responses

Demographic Category	n (%)
Sex	
Male	223 (37.1)
Female	370 (61.6)
Prefer not to say	8 (1.3)
Number of years practicing	
Less or equal 5 years	133 (22)
6 to 10 years	99 (16.4)
>10 years	372 (61.6)
Setting of current practice	
Hospital	155 (25.7)
Community	399 (66.2)
Other	49 (8.1)
Province of current practice	
Alberta	253 (42.0)
Ontario	309 (51.3)
British Columbia	10 (1.6)
Saskatchewan	8 (1.3)
Quebec	8 (1.6)
Other	14 (2.3)

Figure 1: Canadian Pharmacists' Comfort in Epilepsy Management Survey Responses

Figure 2: Canadian Pharmacists' Epilepsy Management Needs Assessment

Figure 3: Average Knowledge Score of Pharmacists Stratified by Practice Setting and Years of Experience
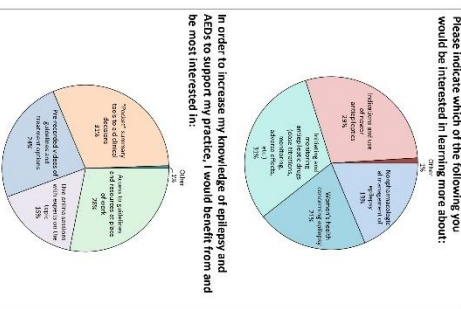
- A total number of 605 completed responses were obtained
- Participants reported high comfort in counselling patients, answering questions and checking prescriptions. Conversely, majority selected the opposite when asked about therapeutic drug monitoring and tapering of AEDs.
- A lower reported comfort level was correlated with lower scores on the knowledge component of the survey
- Participants indicated interest in many types of educational tools including "pocket" summaries of guidelines
- The overall average score on the knowledge component was 57.6±19.1% (n=602)
- Our analysis shows hospital practice, recent graduation and experience in a neurology-related practice to be independent predictors of higher scores.

CONCLUSIONS

- Canadian Pharmacists displayed knowledge and comfort in certain aspects of epilepsy management such as dispensing and counselling with significant gaps in knowledge in other areas. Specifically, significant gaps exist in skills and concepts more specialized to epilepsy management, such as TDM, generic substitutions, women's health and withdrawing from AED therapy.
- Pharmacists indicated a need and interest in epilepsy education tools development
- In order to strengthen pharmacists' comfort and knowledge in epilepsy management, future studies aimed at the development of pharmacy-specific epilepsy educational support tools are needed.

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Predicting symptom trajectories among ambulatory cancer patients receiving anticancer treatment using machine learning approaches: A feasibility study

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Background

- **Machine learning (ML)** approach can predict symptom trajectories which could allow clinicians to prevent worsening symptoms at point-of-care using preventive interventions and personalized symptom management advice.

Objective

- Examine the feasibility of developing ML models to predict cancer-related symptoms of fatigue, pain interference, anxiety, depression, nausea and vomiting, as well as physical and cognitive function.
- Implement ML into a clinician-accessible dashboard for displaying symptom severity and predicted future events.

Methods

- Diagnosed cancer patients completed a series of NIH **PROMIS® questionnaires** at the Chao Family Comprehensive Cancer Center (UCI IRB #20216431) on various cancer-related symptoms including fatigue, pain interference, anxiety, depression, nausea and vomiting, as well as physical and cognitive function.
- **PROMIS symptom scores** are generated with each questionnaires representing the **severity of symptoms.**
- If a patient used the toolkit on multiple visits, we rely on **prior visit data** to predict the PROMIS symptom scores of **the subsequent visit.**
- The ML models were fed with features from the prior visit, including:

Baseline survey data	PROMIS scores from the previous visit
Clinical characteristics	Routine clinical biomarkers obtained via the UC Health Data Warehouse using the UCI Health Honest Broker service

- **Linear Regression, Support, Vector Regression, Random Forest Regression, and Gradient Boosting Regression** were employed on processed data.
- Please refer to Figure 1 for the diagrammatic representation of the study design.

Collect Independent Variables
baseline survey data, clinical characters, and routine clinical biomarkers of each visit

→ **Data Cleaning and Feature Selection**
Remove non-significant features and deal with missing values

→ **Modeling**
Predict Symptom scores of Next Visit with a series of Machine Learning regression Models

→ **Model Evaluation with R squared**

Collect Target Variable
PROMIS symptom scores in the subsequent visit

Figure 1. Methodology

Results

- A total of 289 patient visit record, of which 144 contained data of a subsequent visit necessary for model development.
- Model performance evaluated using R² values is reported in Table 1. **Linear regression consistently outperformed other models for all target symptoms.**
- Table 2 describes the top five significant features of the linear regression model necessary for accurate predictions. **They vary depending on the symptom assessed and comprise immuno-oncology agents, clinical biomarkers and sociodemographic characteristics.**

Table 1. R² on Prediction Models and Dependent Symptom Variables

R² Performance	Linear Regression	SVR(linear kernel)	Random Forest Regression	Gradient Boosting Regression
Anxiety	0.55	0.45	0.07	-0.01
Depression	0.57	0.48	0.15	0.14
Cognitive Function	0.46	0.35	0.23	0.05
Physical Function	0.54	0.47	0.20	-0.04
Fatigue	0.48	0.43	0.17	0.09
Pain Interference	0.39	0.28	0.20	0.02
Nausea and Vomiting	0.42	0.30	0.23	0.12

Abbreviation(s): SVR: support vector regression

Table 2. Top Significant Features of the Best Performing Linear Regression Model

R² Performance	Top five features (in order, from left to right)
Anxiety	**Nivolumab**, red blood cell count, albumin, creatinine, exposure to immunotherapy
Depression	**Durvalumab**, creatinine, red blood cell count, exposure to immunotherapy, race & ethnicity
Cognitive Function	**Nivolumab**, pembrolizumab, sex, cemiplimab, atezolizumab
Physical Function	**Cemiplimab**, atezolizumab, ipilimumab, red blood cell count, creatinine
Fatigue	**Creatinine**, race & ethnicity, marital status, cemiplimab, atezolizumab
Pain Interference	**Red blood cell count**, nivolumab, creatinine, sex, marital status
Nausea and Vomiting	**Nivolumab**, creatinine, red blood cell count, sex, albumin

Conclusions

- The feasibility of utilizing ML to predict medical symptoms has been demonstrated in our study.
- Various models may perform differently with some models more effective than others, there is no one-size-fits-all solution.
- Various features are better at predicting some but not other symptoms.

Future Directions

- We will continue to refine current models through parameter tuning and independent feature selection targeting different symptoms.
- The set of clinically relevant features will also expand to incorporate cancer diagnoses and anticancer drugs.
- Finally, we will explore the prediction of other health outcomes such as unplanned healthcare utilizations.

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Efficacy of Tinnitus Retraining Therapy (TRT) on Tinnitus Patients: A Meta-Analysis

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BACKGROUND

- Tinnitus is an audiological disorder, prevalent in 10% of the UK population, it occurs when sound is perceived in the absence of an actual external stimuli.[1,2]
- Tinnitus is described as a hissing, buzzing, sizzling or whistling sound.[3]
- There are two classifications: subjective (heard by individual only) or objective (heard by examiner also).[4]
- Impacts of tinnitus may be: impaired concentration, social isolation, insomnia, anxiety, depression and suicide (rarely).[3]
- There is no known cure for tinnitus.[4]
- Annual NHS bill of £750m.[5]
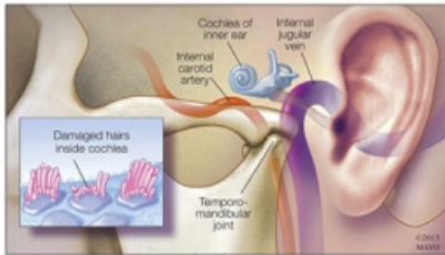
Credit: Mayoclinic, Source: 'What is tinnitus', Hearing Health Foundation:https://hearinghealthfoundation.org/what-is-tinnitus

OBJECTIVE

The aim of this study was to evaluate the efficacy of TRT versus usual (standard) care in accordance with the PRISMA guidelines on transparent reporting of systematic reviews and meta-analyses.

METHOD

Literature search	PubMed, Cochrane library and ClinicalTrials.gov were searched (October and December 2019).
Eligibility criteria	Records were screened against a predefined eligibility criteria set using the PICOS tool (table 1).
Data extraction	Data used from THI scores assessed after 12-months of TRT initiation were extracted.
Performance of meta-analysis	A random effects meta-analysis was carried out to evaluate efficacy of TRT and validity using RevMan.[6]
Critical appraisal	A risk of bias assessment was carried out to assess six domains of the eligible studies.
Study presentation	Study was reported using the PRISMA guidelines and follows the journal style for the 'Lancet'.

PICOS [7]

Population	Intervention	Comparison	Outcome	Study design
Adults (>16 years) with chronic, bothersome tinnitus	TRT involving counselling AND acoustic therapy	Usual or standard care without the use of sound therapy	Tinnitus Handicap Inventory (THI) scores at 12-months after initiation	Randomised controlled trials (RCTs)

Table 1: Predefined eligibility criteria using the PICOS tool

RESULTS

- Four RCTs met the PICOS criteria and were eligible for the quantitative meta-analysis.
- TRT is more effective than usual care (p=0.03) for reducing tinnitus severity (fig. 2).
- Sensitivity analysis showed otherwise (fig 3).
- All included studies had either 'unclear' or 'low' risk of bias.

Figure 1. PRISMA flow diagram showing search and selection of included trials. Source: (see below)[8]
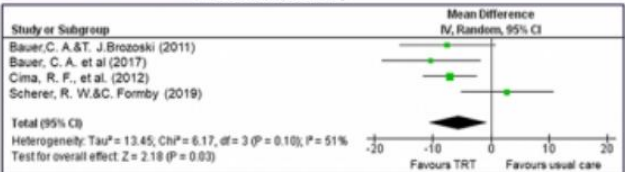
Figure 2: Forest plot showing meta-analysis of four RCTs which investigated TRT vs. usual care.
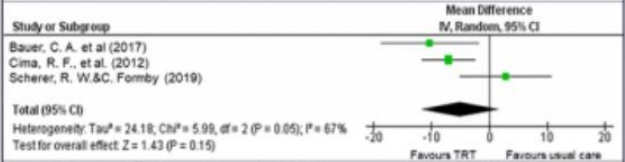
Figure 3: Forest plot showing sensitivity analysis, following removal of Bauer et al (2011) study.

Results of this meta-analysis have:
1) Statistically evaluated the efficacy of TRT.
2) For the first time synthesised data from RCTs involving TRT
3) Critically analysed present RCTs for TRT.
4) Systematically extracted, synthesised and analysed the data.

Key limitations of this meta-analysis include:
1) Moderate heterogeneity due to RCT differences.
2) Only four RCTs were included, more trials would enable results to reflect the general population further.
3) Sensitivity analysis has indicated a different outcome.
4) Adverse effects taken into account.

CONCLUSION AND FUTURE WORK

- TRT improves quality of life, and reduces tinnitus associated distress.
- Cost-effectiveness of TRT needs to be researched into.
- More stringent measures need to be in place for TRT RCTs.
- Tinnitus is a disorder that requires more funding and research for development of breakthrough therapies.
- Patient preference and adherence should be considered in future works.
- Development of a single tool to assess the various impacts of tinnitus may be beneficial for both patients and healthcare professionals.

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1.

UCI School of Pharmacy & Pharmaceutical Sciences

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CHAPMAN UNIVERSITY

Impact of the COVID-19 Pandemic on Opioid Overdose in California: An Analysis of Emergency Department Visit Trends from 2018 to 2022

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Background

- The COVID-19 pandemic has had a devastating impact on mental health across the United States, including California, which resulted in the highest rates of opioid overdose emergency department (ED) visits in 2020.

- This was likely the consequence of excessive stress and worsening mental health due to pandemic-associated lockdowns and isolation, compounded by the difficulties in access to Medications for Opioid Use Disorder.

- As California slowly returned to pre-pandemic normalcy in 2021 and 2022, it remains uncertain whether the rates of opioid overdoses have slowed down over time.

Objective and Hypothesis

- Our objective was to compare the trends of ED visits associated with opioid overdoses in the period before (Jan 2018 to Dec 2019) and during the pandemic (Apr 2020 to Dec 2022). A washout period between Jan 2020 and Mar 2020 was implemented due to widespread uncertainty regarding the nature of the pandemic during that timeframe.

- We hypothesize that opioid overdose ED visit rates have worsened given the challenges that individuals faced during the pandemic while overcoming opioid addiction.

Methods

- **Data Source:** This analysis uses the *University of California (UC) Health Data Warehouse*, a database of electronic health records from the six UC health centers. IRB review was not required for this de-identified data analysis.

- **Opioid overdose ED visits** were queried using SQL and defined using ICD-10-CM (F11 codes, and T40.0*, T40.0*, T40.1*, T40.2*, T40.3*, T40.4*, T40.6*), and then classified by types of opioids involved: heroin (T40.1*), prescription opioids (T40.2* or T40.3*), and synthetic opioids other than methadone (T40.4*).

- **Statistical Analysis:** *Interrupted time analysis* was performed to estimate the immediate (level) change and change in time trend (trend change) for each outcome with negative binomial regression adjusted for first order autoregression and using all-cause ED visit counts as the offset variable. Effect sizes were presented as rate ratios and 95% confidence intervals. Analyses were tested with α=.05 and completed with Stata v16.1.

Results

- Trends in opioid overdose ED visit rates were significantly different between the periods prior to and during COVID-19 *(Figure 1)*.

- *As of December 2022, prescription and synthetic opioids (Figure 1A-C) overdose ED visit rates were higher than pre-pandemic trends.* In contrast, heroin overdose *(Figure 1D)* visits saw a downward trend during the pandemic.

(A)

Parameters	Rate ratios (RRs)	% change	95% confidence intervals (CIs)	P
Slope pre-COVID (/mth)	1.01	+1%	1.006–1.02	<0.001***
Immediate change	1.15	+15%	1.02–1.29	0.020*
Slope COVID (/mth)	0.995	-0.5%	0.991–1.00	0.020

(B)

Parameters	Rate ratios (RRs)	% change	95% confidence intervals (CIs)	P
Slope pre-COVID (/mth)	1.01	+1%	1.002–1.02	0.021*
Immediate change	1.44	+44%	1.10–1.89	0.008**
Slope COVID (/mth)	1.01	+1%	0.998–1.02	0.116

(C)

Parameters	Rate ratios (RRs)	% change	95% confidence intervals (CIs)	P
Slope pre-COVID (/mth)	1.05	+5%	0.998–1.11	0.060
Immediate change	1.69	+69%	0.68–4.16	0.256
Slope COVID (/mth)	1.04	+4%	1.02–1.06	0.001**

(D)

Parameters	Rate ratios (RRs)	% change	95% confidence intervals (CIs)	P
Slope pre-COVID (/mth)	1.02	+2%	1.006–1.03	0.006**
Immediate change	1.20	+20%	0.86–1.67	0.282
Slope COVID (/mth)	0.92	-8%	0.90–0.93	<0.001***

Figure 1. (A) Total opioid overdose ED visit rates increased immediately after Mar 2020 before reaching statistical significance. **(B)** Similar trends were observed with prescription opioids, with a step before plateauing after Mar 2020. In contrast, ED visit rates for synthetic opioids poisoning **(C)** were increasing steadily every month, unlike heroin **(D)** which was observed with monthly reduction. No immediate increase in ED visit rates was observed for both types of opioids after Mar 2020.
(*p<0.05, **p<0.01, ***p<0.001)

Discussion

- *The COVID-19 pandemic brought to light the urgent need for multilevel innovative approaches to aid against the opioid epidemic in California.* In particular, the pandemic has facilitated the worsening of trends related to synthetic and prescription opioids overdoses across the UC health centers with little signs of improvement as of December 2022.

- In 2023, numerous policy changes have been made to increase access to Medications for Opioid Use Disorder (MOUD) for reducing opioid overdose complications and deaths: (1) the removal of the X-Waiver, allowing physicians to prescribe buprenorphine in clinics without extensive training and registration, and (2) the FDA approval of Narcan®, the first over-the-counter naloxone nasal spray. *Interventions that enhance facilitators and reduce barriers (e.g., telehealth prescribing, education, reducing stigma to seeking treatment, harm reduction services) will ensure that these policies work as intended (first responders to opioid overdose events).*

- *Within University of California, there is immense potential for increased cross-institution collaborations* to lead and address this highly complex public health issue using multilevel coordinated strategies (patient, family, clinicians, community and institutions).

- Using the UC Health Data Warehouse, future studies can investigate the risks of repeated opioid overdose admissions, create a dashboard for monitoring admission trends across UC Health institutions, develop prediction models for risk of opioid addiction and overdose events, and evaluate trends in stimulant-related overdose events (methamphetamine and cocaine).

Conclusions

- As of December 2022, rates of prescription and synthetic opioids overdoses were higher than pre-pandemic trends. *These findings represent a call to action for an increase in California-focused research studies to arrest this worsening opioid epidemic as we return to pre-pandemic normalcy.*

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2.

CONSTRUCTION & SIMULATION ANALYSIS OF AN IMPROVED ACTIN FILAMENT MODEL

INTRODUCTION

HOLMES 2010 MODEL

METHODS

REFERENCES

RESULTS

CONCLUSIONS

ACKNOWLEDGEMENTS

OAK RIDGE

3.

PIGS IN SPACE: EFFECT OF ZERO GRAVITY AND AD LIBITUM FEEDING ON WEIGHT GAIN IN CAVIA PORCELLUS

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ABSTRACT:

One ignored benefit of space travel is a potential elimination of obesity, a chronic problem for a growing majority in many parts of the world. In theory, when an individual is in a condition of zero gravity, weight is eliminated. Indeed, in space one could conceivably follow an ad libitum feeding and never even gain a gram, and the only side effect would be the need to upgrade one's stretchy pants/exercise pants"). But because many diet schemes start as very good theories only to be found to be rather harmful, we tested our predictions with a long-term experiment in a colony of Guinea pigs (Cavia porcellus) maintained on the International Space Station. Individuals were housed separately and given unlimited amounts of high-calorie food pellets. Fresh fruits and vegetables were not available so were not offered. Every 30 days, each Guinea pig was weighed. After 5 years, we found that individuals, on average, weighed nothing. In addition to weighing nothing no weight appeared to be gained over the duration of the protocol. If space continues to be gravity-free, and we believe that assumption is sound, we believe that sending the overweight — and those at risk for overweight — to space would be a lasting cure.

INTRODUCTION:

The current obesity epidemic started in the early 1960s with the invention and proliferation of elastane and related stretchy fibers, which released wearers from the rigid constraints of clothes and permitted monthly weight gain without the need to buy new outfits. Indeed, exercise today for hundreds of million people involve only the act of wearing stretchy pants in public, presumably because the constrictive pressure forces fat molecules to adopt a more compact tertiary structure (Xavier 1965).

Luckily, at the same time that fabrics became stretchy, the race to the moon between the United States and Russia yielded a useful fact: gravity in outer space is minimal to nonexistent. When gravity is zero, objects cease to have weight. Indeed, early astronauts and cosmonauts had to secure themselves to their ships with seat belts and sticky boots. The potential application to weight loss was noted immediately, but at the time travel to space was prohibitively expensive and thus the issue was not seriously pursued. Now, however, multiple companies are developing cheap extra-orbital travel options for normal consumers, and potential travelers are also creating news ways to pay for products and services that they cannot actually afford. Together, these factors open the possibility that moving to space could cure overweight syndrome quickly and permanently for a large number of humans.

We studied this potential by following weight gain in Guinea pigs, known on Earth as fond of ad libitum feeding. Guinea pigs were long envisioned to be the "Guinea pigs" of space research; on Earth, too, so they seemed like the obvious choice. Studies on humans are of course desirable, but we feel this current study will be critical in acquiring the attention of granting agencies.

MATERIALS AND METHODS:

One hundred male and one hundred female Guinea pigs (Cavia porcellus) were transported to the International Space Laboratory in 2010. Each pig was housed separately and deprived of exercise wheels and fresh fruits and vegetables for 48 months. Each month, pigs were individually weighed by duct-taping them to an electronic balance sensitive to 0.0001 grams. Back on Earth, an identical cohort was similarly maintained and weighed. Data was analyzed by statistics.

RESULTS:

Mean weight of pigs in space was 0.0000 +/- 0.0002 g. Some individuals weighed less than zero, some more, but these variations were due to reaction to the duct tape, we believe, which caused them to be alarmed push briefly against the force plate in the balance. Individuals on the Earth, the control cohort, gained about 240 g/month (p = 0.0002). Males and females gained a similar amount of weight on Earth (no main effect of sex), and size at any point during the study was related to starting size (which was used as a covariate in the ANCOVA). Both Earth and space pigs developed substantial dewlaps (double chins) and were lethargic at the conclusion of the study.

CONCLUSIONS:

Our view that weight and weight gain would be zero in space was confirmed. Although we have not replicated this experiment on larger animals or primates, we are confident that our result would be mirrored in other model organisms. We are currently in the process of obtaining necessary human trial permissions, and should have our planned experiment initiated within 80 years, pending expedited review by local and Federal IRBs.

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NRF

BLACK HOLE DIET PLANS

SPACE EXES

THE HIGH FRUCTOSE SUGAR ASSOCIATION

4.

O⁶-Benzylguanine Inhibits Tamoxifen Resistant Breast Cancer Cell Growth and Resensitizes Breast Cancer Cells to Anti-Estrogen Therapy

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Abstract

Endocrine therapies using anti-estrogens are least toxic and very effective for breast cancers. However, tumor resistance to tamoxifen remains a stumbling block for successful therapy. Based on our recent study on the involvement of the DNA repair protein MGMT in pancreatic cancer (Clin Cancer Res, 15, 6087, 2009), here, we investigated whether MGMT overexpression mediates tamoxifen resistance. Specifically, we determined whether administration of MGMT inhibitor (O⁶-benzylguanine [BG]) at a non-toxic dose alone or in combination with the anti-estrogens (tamoxifen/fulvestrant) curtails human tamoxifen resistant breast cancer cell growth. Further, we also determined whether BG sensitizes breast cancers to tamoxifen using tamoxifen resistant cells.

MGMT expression was found to be increased in breast cancer cells relative to normal breast epithelial cells. Also, MGMT levels were significantly higher in tamoxifen resistant MCF-7 compared to the parent cells. Silencing of the ER-α expression using a specific siRNA resulted in augmentation of MGMT mRNA and protein levels by 2 fold. We also observed an inverse correlation between MGMT and p53 levels in breast cancer cell lines; moreover, p53 downregulation was accompanied by decreased MGMT expression. Other experiments showed that BG alone or BG in combination with tamoxifen or fulvestrant alone increased and decreased the same respectively. However, all these treatments increased the p21/53 and protein expression significantly; BG inhibited tamoxifen resistant breast cancer growth in a dose-dependent manner and it also resensitized resistant breast cancer cells to anti-estrogen therapy (TAM/ICI). These combinations also enhanced the cytochrome C release and the PARP cleavage, indicative of apoptosis. In breast cancer xenografts, BG alone or a combination of tamoxifen with BG or fulvestrant with BG significantly inhibited tumor growth. BG and the expression of MGMT were decreased while the p21/53, ki-67 and the immunohistochemistry showed that that BG and the combination of tamoxifen or fulvestrant with BG increased p21/53 staining. These findings suggest that MGMT inhibition may provide a novel and effective approach for overcoming tamoxifen resistance.

Introduction

Recent advances in breast cancer research have identified key pathways involved in the repair of DNA damage induced by chemotherapeutic agents. The ability of cancer cells to recognize DNA damage and initiate DNA repair is an important mechanism for therapeutic resistance and has a negative impact on efficacy. A number of DNA-damaging alkylating agents attack the nucleophilic O⁶ position on guanine, forming mutagenic and highly cytotoxic interstrand DNA crosslink. The DNA repair enzyme O⁶-alkylguanine DNA alkyltransferase (AGT), encoded by the gene MGMT, repairs alkylation at this site and is responsible for protecting both tumor and normal cells from alkylating agents. MGMT is expressed constitutively in normal cells and tissues. In breast tumors, MGMT gene expression is elevated and levels are up to 4-fold higher than in the normal breast. Interestingly, in 1991, Pegg, Moschel, and Dolan observed that O⁶ benzylguanine (BG) inhibited AGT and potentiated the cytotoxicity of both chloroethylating agents and methylating agents. In a series of important observations, they fully characterized the interaction between BG and AGT and its therapeutic impact. They showed that BG binds AGT, transferring the benzyl moiety to the active-site cysteine [20]. The reaction is very rapid and more potent than any other alkyl group to DNA in living cells and reacts directly with both cysteine and nuclear AGT. Because BG is an inactivator of MGMT which results in the covalent transfer of benzyl group to the active site cysteine, the MGMT protein is degraded after each reaction. Thus the stoichiometric reaction mechanism effectively depletes the AGT content in tumors and the associated repair of alkylation damage. BG is currently undergoing clinical trials in various cancers to increase the efficacy of alkylating agents.

Interestingly, several observations suggest an inverse correlation between the levels of MGMT and p53 tumor suppressor proteins where wild-type p53 suppresses transcription of human MGMT expression. Unfortunately, p53 function is often inactivated or suppressed in human cancers; therefore, restoration of wt-p53 activity is essential for the success of some treatments. However, whether or not this is mediated by suppression of MGMT expression has yet to be determined. To date, the cross-talk between MGMT and ER-alpha (and the link to p53 expression) has not been explored in the highly utilized, most commonly used treatment for patients with tamoxifen resistant breast tumors. The anti-estrogen tamoxifen is the most commonly used treatment for patients with estrogen receptor positive breast cancers. Although a significant benefit from tamoxifen is gained, in most settings, resistance to this endocrine therapy presents a serious clinical problem. The primary goal of present study was to investigate the mechanisms of anti-estrogen drug resistance and to design new therapeutic strategies for circumventing this resistance. The results show that MGMT expression is increased in TAM-resistant breast cancers and inhibition of MGMT by BG significantly improves TAM-sensitivity.

Results

Prolonged Treatment of Tamoxifen Increases MGMT Expression. We developed a tamoxifen resistant MCF-7 cell line by using prolonged treatment of tamoxifen on the parental ER-positive breast cancer cell line. Prolonged treatment of tamoxifen-resistant MCF-7 cells proliferate at rates similar to the parental MCF-7. Prolonged treatment of tamoxifen onto MCF-7 cells increased MGMT expression compared to parental MCF-7 cells by 2 fold (Fig.1).

Knocking Down ERα Enhances MGMT Expression in Tamoxifen Resistant Breast Cancer Cells. It is not known whether ERα and MGMT transcriptionally regulate each other in tamoxifen resistant breast cancer cells. We therefore investigated whether down regulation of ERα has any effect on endogenous MGMT expression in these cells. As expected, downregulation of ERα using specific siRNA significantly reduced ERα protein levels in these cells. Western blot analysis was performed and the results in the left panel (Fig. 2A) shows that silencing of ERα increases MGMT expression in these cells, and interestingly, the results in the right panel (Fig.2B) show increased MGMT mRNA levels were increased as assessed by qRT-PCR. These data suggest that ERα-mediated signaling functions to repress MGMT gene expression in breast cancer cells.

Transcriptional Regulation Between MGMT and p53 Previously, it was reported that p53 negatively regulates MGMT in breast cancer cells. Therefore, we addressed whether or not silencing the p53 enhances endogenous MGMT transcription. Tamoxifen resistant MCF-7 cells were transfected with either p53 siRNA (p53-KD) (Fig.2C) or MGMT siRNA (MGMT-KD) (Fig.2D) along with Non-specific siRNA (NS). MGMT expression was consistently increased in p53 knock down cells, with different experiments showing a fold augmentation (Fig. 2A) and as expected, knocking down MGMT decreased MGMT transcription where as p53 mRNA levels were unaffected at the transcriptional level. These results confirm that p53 can regulate MGMT in breast cancer cells.

Figure 1. MCF-7 parental and tamoxifen resistant MCF-7 cell protein were isolated and MGMT expression was detected by western blot. MGMT expression was significantly increased in MCF-7 parental cells.

MCF-7 cells
TAM resist. MCF-7

O⁶-Benzylguanine Plays a Dual Role in Tamoxifen Resistant MCF-7 Cells. Contrasting with the experiments above, next, we studied whether or not knocking down MGMT has any effect on ERα transcription as expected, knocking down MGMT silencing, (Fig.2E). These data demonstrate that BG has the ability to attenuate the not only the MGMT, but also the ERα transcription, indicating a possible dual role for MGMT blockers in these breast cancer cells.

Figure 2. (A) Tamoxifen resistant MCF-7 cells were transfected with ERα siRNA (ERα-KD) and NS siRNA (control) (NS), and mRNA were isolated and ERα and MGMT expression was determined by qRT-PCR. MGMT transcription was significantly increased in ERα knock down cells. (B) Total protein were isolated and ERα and MGMT expression was determined by western blot analysis. MGMT protein was significantly increased in ERα knock down cells. (C) Tamoxifen resistant MCF-7 cells were transfected with p53 siRNA (control) (NS), and mRNA were harvested for qRT-PCR. (D) Total RNA was isolated from non-specific (control) and MGMT siRNA (control) knock down cells. (E) Total RNA was isolated from non-specific siRNA (NS) (control) and MGMT siRNA (control) knock down cells, and ERα transcription was determined by qRT-PCR. ERα transcription was significantly decreased in tamoxifen resistant MCF-7 breast cancer cells.

**O⁶-Benzylguanine Modulates p53 Down-Stream Targeted Protein Expressions: ** Encouraged by the results reported, we investigated the effect of combination therapy on endogenous MGMT, p53, and ERα protein expressions. As expected, BG decreased MGMT expression, while combination with tamoxifen or ICI combined with BG significantly decreased both MGMT and ERα expressions, where BG alone or in combination with tamoxifen alone and ICI alone increased p53 expression. Also, we determined the effect of BG on p53 mediated cell cycle regulation, apoptosis in tamoxifen resistant cancer cells. All these treatments significantly increased the p21 protein expression (Fig.2B). PUMA expression was also increased with these treatments. Hence, PUMA may have transduced its death signal through mitochondria, cytochrome C is released (Fig.3B), and apoptosis was triggered in these cells in presence of combination therapy. PARP cleavage is seen in BG treated cells in presence of staurosporin as an indicative of apoptosis by modulating p53 function.

Figure 3. (A) Tamoxifen resistant MCF-7 breast cancer cells were treated in presence or absence of BG (50 μg) alone or in combination with 4-OH-TAM and ICI. Total protein expression was harvested and western blot analysis was performed. (B) Cytochrome C, PUMA, and p21 were determined by western blot analysis. (C) Tamoxifen resistant MCF-7 cells were treated with or without BG for 48h and later treated with staurosporin (5 μM/L) for 6 hr PARP cleavage was determined by western blot analysis.

O⁶-Benzylguanine Enhances p21 Transcriptional Activity in Tamoxifen Resistant Breast Cancer Cells: In order to investigate the effect of BG on p53 functions, we performed luciferase reporter assays. Tamoxifen resistant MCF-7 breast cancer cells were transfected with p21 luc promoter and the control with BG (target gene of p53). These results clearly demonstrate that BG significantly enhanced p21 transcriptional activity by 4-5 fold in these cells (Fig.4D).

Figure 4. Tamoxifen resistant MCF-7 breast cancer cells were treated for presence or absence of BG (50 μg) cells were harvested and RNA was isolated. (A) MGMT and ERα transcription was determined by qRT-PCR. (B) p53 transcription was determined by qRT-PCR. and (C) p21 target gene transcription was determined by qRT-PCR. p53 and p21 transcription, BG increased PUMA and p21 transcription. (D) p21 Luc transfection with p21 target gene activity was significantly increased by BG in these cells.

O⁶-Benzylguanine Inhibits Tamoxifen Resistant Breast Cancer Cell Sensitivity to Anti-Estrogen Therapy (TAM/ICI): Detailed necropsy revealed that all the mice had tumors in the breast. The data summarized in Table 1 show that the daily BG alone or in combination with twice weekly tamoxifen/ICI significantly decreased median tumor volume and weight as compared with that seen in tamoxifen/ICI treated and control mice. The combination of BG with tamoxifen or ICI produced the greatest decrease in median tumor volume as compared with control mice (89.99 mm³, 9.33 mm³ (TAM+BG), respectively; p< 0.0001). Tumor weight was also significantly reduced in mice treated with combination therapy as compared with control mice weight (TAM+BG), respectively; p<0.00001). Body weight was not changed among all treatment groups as compared with control mice. No visible liver mechanism were present (enumerated with the aid of a dissecting microscope) in all treatment groups.

Figure 5. Tumors were harvested from control mice and mice treated with tamoxifen/ICI, BG, or both tamoxifen/ICI and BG. The tumors immunostained for the expression of MGMT, ERα. BG alone or in combination with tamoxifen or ICI had a significant decrease in the expression of MGMT, ERα respectively. (A) p53 expression was increased in mice treated with BG either alone or in combination with tamoxifen/ICI as compared to control. The expression of p21 was increased in all these treatment groups compared to control. Representative samples (40X) are shown.

O⁶-Benzylguanine Inhibits Tamoxifen Resistant Breast Cancer Cell Growth and Increase Resistant Breast Cancer Cell Sensitivity to Anti-Estrogen Therapy (TAM/ICI).

Histology and IHC Analysis: We next determined the in vivo effects of BG (alone or in combination) with tamoxifen/ICI. Tumors harvested from different treatment groups were processed for routine histological and IHC analysis. Tumors from mice treated with BG alone or in combination with tamoxifen/ICI exhibited a significant decrease in MGMT, ERα, ki-67 as compared with tumors treated with tamoxifen/ICI alone or control group. p53 expression was not much altered in these treatment groups. In sharp contrast, the expression of p21 was significantly increased in tumors from mice treated with BG either alone or in combination with tamoxifen/ICI. The images were analyzed by Image J (NIH) and MGMT, ERα, p53, p21 and ki-67 expressions were quantified by the ImmunoRatio plugin (Fig.5).

Conclusions

1. In the present study, we observed that prolonged treatment with anti-estrogens causes drug resistance by inducing the DNA repair protein O⁶-methylguanine DNA methyltransferase (MGMT).

2. Decreasing the expression of MGMT to BG sensitized these cells to anti-estrogen therapy (tamoxifen and ICI 182/780).

3. We also observed that combination therapy of anti-estrogens and MGMT blockers not only overcame the MGMT derived drug (tamoxifen and ICI) resistance but also increased the efficacy of anti-estrogen therapy by inducing estrogen receptor expression and restoration of the functional activity of p53 in tamoxifen-resistant breast cancer cells.

4. Combination therapy inhibited tamoxifen resistant breast tumor growth in vivo.

Acknowledgements

Pigs in space: why is this poster terrible?

1. Too much _____ (I've been on mission to push for 800 words).
2. Background image is _____ (distracts from illustrations).
3. Text box backgrounds are _____, which makes text really hard to read.
4. Text box backgrounds are all different _____, for no reason.
5. Text boxes are different _____ (hard to follow flow of poster).
6. Some text boxes too _____ (aim for 45-65 characters per line).
7. Text boxes not separated from each other by pleasing "_____" space.
8. Text box edges not _____.
9. Text justified, which causes bad inter-word _____. Also makes reading harder (brain *uses* jaggedness of left-justified text).
10. _____ are distracting, useless, crowd title.
11. Title is in all _____, which is harder to read
12. Title is _____, which obscures style conventions.
13. Author _____ and colour are annoying (comic sans should be reserved for comic books).
14. Author font color is too _____ relative to other text.
15. Results are presented in sentences instead of visually with _____.
16. Section headers have too much _____ (big font, bolded, italicized, underlined, *and* coloured!). Choose one.
17. Terrible _____ of Guinea pig on scale. Need one of the actual set up (pigs eating while weightless, for example).
18. Inclusion of an _____ consumes space needlessly. _____ sections should be banned from posters. Posters ARE an _____.
19. Plus the science is _____! (Bad science is correlated with bad graphic design, by the way

Help: here are the words to place
text
formatting
abstract (x3)
caps
loud
distracting
terrible
dark
white
charts
spacing
aligned
wide
colours
widths
italicized
graphic
logos

WORKSHOP 3: CONVERTING AN ARTICLE INTO A POSTER

RESEARCH

Baseline Assessment of Systemic Racism Education inPharmacy Curricula

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Objective. To determine, by survey, the inclusion of systemic racism education in US Doctor of Pharmacy (PharmD) curricula and identify barriers and facilitators to addressing this content.

Methods. A survey was developed and distributed to curricular representatives at US colleges and schools of pharmacy. The survey assessed inclusion of systemic racism education in curricula, facultyinvolvement in teaching systemic racism content, barriers to adding systemic racism content in curricula,and future curricular plans. Data were analyzed using descriptive statistics for institutional background information, curricular content, and barriers to inclusion. Relationships between the inclusion of systemic racism content at public versus private programs were examined, and associations between traditional and accelerated programs were assessed.

Results. Fifty-eight colleges and schools of pharmacy provided usable responses. Of the respondents, 84% indicated that teaching systemic racism content and its impact on health and health care was a lowpriority. For 24% of respondents, systemic racism content was not currently included in their curriculum,while 34% indicated that systemic racism content was included in one or more courses or modules butwas not a focus. Despite systemic racism content being offered in any didactic year, it was rarely includedin experiential curricula. Top barriers to inclusion were lack of faculty knowledge and comfort with con- tent and limited curricular space. No significant differences were found between program types.

Conclusion. Based on the current level of systemic racism education and barriers to inclusion, facultyneed training and resources to teach systemic racism concepts within pharmacy curricula. The inclusionof systemic racism concepts and guidance in the Accreditation Council for Pharmacy Education's Accreditation Standards could help to drive meaningful change and promote health equity.

Keywords: systemic racism, curricular integration, pharmacy education, social determinants of health, health equity

INTRODUCTION

The World Health Organization defines the social determinants of health as, "… the circumstances in which people are born, grow up, live, work and age, and the systems put in place to deal with illness. These circum- stances are in turn shaped by a wider set of forces: economics, social policies, and politics."[1] These factors have been identified as the root causes of health disparities, the potentially avoidable differences in health between groups of people who are more and less advantaged socially.[2,3] In the past two decades, there has been a marked increase in initiatives to address social determinants of health in the United States. Education related to social determinants of health is needed to prepare the future health care work- force to meet the health care needs of individual patients and address disparities in the communities that they serve.[4] In 2016, the National Academies of Sciences, Engineering, and Medicine called for and developed a framework to educate health professionals regarding social determinants of health to provide more effective strategies for improving health and health care for under-served populations.[5] Specific to pharmacy education, the Accreditation Standards and guidelines put forth by the Accreditation Council for Pharmacy Education (ACPE) recognize the need for social determinants of health education and require that Doctor of Pharmacy (PharmD) graduates are able to describe how population-based care influences patient care (Standard 2.4) and recognize social determinants of health to diminish inequities in access to quality care for patients (Standard 3.5).[6]

Systemic racism is the culmination of policies, laws, rules, norms, and customs enacted by organizations and societal institutions that advantage White people as a group and disadvantage groups of color.[7] Systemic racism is a key but often underemphasized concept under the social determinants of health umbrella.[8] Healthy People 2030 divides social determinants of health into five inter- related domains: economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context.[8] In the United States, each of these domains is deeply rooted in systemic racism.[8] It is imperative for health care providers to understand how the health of communities of color and individuals has been impacted by years of redlining, segregation, exclusion from wealth-building programs such as the GI Bill, disparate educational institutions and health care access, unequal medical treatment, discrimination, bias, mass incarceration, police violence, and housing and income inequalities.[9,10] Furthermore, on an individual level, the experiences of racism have been found to lead to physiological and cardiovascular stress responses and are associated with multiple indicators of poorer physical and mental health status.[11-14]

However, within the health sciences curricula, differences in disease state morbidity and mortality indicators among racial and ethnic groups are often taught without context, and race may be pathologized.[15] The social con-struct of race is also conflated with biology, as seen in the algorithms of various disease states that are presented.[16,17] While there are no characteristics that adequately explain these differences, learners may falsely conclude that health disparities are the result of genetic predisposition, cultural norms, and personal health behaviors. Recognizing the role systemic racism plays in perpetuating these statistics is critical. Treating only the outcome and not the root cause of the crisis leaves patients vulnerable to sustained or repeated exposure to disease and even death. While academic pharmacy has adopted curricular integration of more sweeping topics such as social determinants of health, cultural competency/humility, and implicit bias in recent years, little is known about the explicit inclusion of systemic racism as a key determinant of health in phar macy education.[18-21]

In the spring of 2020, the deaths of George Floyd, Ahmaud Arbery, Breonna Taylor, and so many others served as an inflection point in social justice and racial equity movements in the United States. Coupled with significant racial and ethnic health disparities in the COVID-19 pandemic, organizations, educational institutions, and individuals have sought to evaluate their role and their response in addressing systemic racism. Numerous institutions, including the Centers for Disease

Control and Prevention, the American Medical Association, and a conglomerate of 14 national pharmacy organizations have released statements that declare racism as a serious threat to public health.[22-25] Across the country, three states and over 90 local municipalities have also declared racism a public health crisis or emergency.[26] In July 2020, the House of Delegates for the American Association of Colleges of Pharmacy (AACP) released statements affirming a commitment to diversity, equity, inclusion, and anti-racism and affirmed the organization's support of integrating systemic racism content within the core curriculum.[27]

With recent publications and organizations recognizing racism as a public health crisis and systemic racism as a root cause of racial health inequities in the United States, it is incumbent upon colleges of pharmacy to include or expand their curricula to include education on systemic racism.[28,29] However, the extent to which this content is currently taught within the pharmacy curricula is unknown, as teaching racism as a determinant of health is not included in the current ACPE Standards. The purpose of this study was to provide a multi-institutional assessment of systemic racism education within PharmD curricula. Specifically, this study assessed the extent to which systemic racism education is included in PharmD curricula, how and where it occurs, and barriers and facilitators to addressing this content.

METHODS

The research team comprised seven members of the AACP Health Disparities and Cultural Competency (HDCC) Special Interest Group (SIG). Belmont University's institutional review board granted exempt status for this study. Collaborating faculty filed the study with their respective institutional review boards. A survey was created by consensus of team members but patterned, with permission, after the survey used by Chen and colleagues to evaluate the inclusion of health disparities in the pharmacy curriculum.[18] The resulting instrument was piloted in the seven schools represented among the research team members. Based on the pilot, the working definition of systemic racism was included for reference at the start of each section of the survey, and the survey instrument was further refined. The 28-question finalized electronic sur-vey was built using Qualtrics online survey software (Qualtrics International Inc).

The electronic survey, titled Systemic Racism Education in Pharmacy Curriculum, included questions in four areas: background information about the organizational structure of the institution and current role of the responding faculty; curricular content (if, when, what, where, and how systemic racism was included in the didactic and experiential curriculum); faculty involvement and future curric-ular plans for teaching systemic racism; and barriers to the inclusion of systemic racism content in the curriculum.

Potential US colleges and schools of pharmacy contacts for survey distribution were identified via an AACP-provided list of 141 faculty contacts involved in curricular matters. The list consisted primarily of deans of academic affairs or chairs of curriculum or assessment committees. Any missing data were completed by the team using the institution's website to identify the dean of academic affairs or its equivalent. Any noted inaccuracies or changes in role or employment were corrected by the researchers using either their personal contacts at the college or school of pharmacy or the institution's website.

After finalizing the distribution list, emails were sent to contacts that included the survey link, survey purpose, consent preamble, and notice that completion of the sur- vey was voluntary. Three additional emails were sent to nonresponders only, at two- to three-week intervals. After the third reminder, members of the research team communicated via email or phone with listed faculty or personal contacts at nonresponding colleges and schools of pharmacy to encourage participation. The reminder email pro-vided the faculty member with the letter of invitation, survey link, and a request to forward or complete the survey if they were not the person with knowledge of the curriculum. The data were collected from June through August 2021.

Data were analyzed using SPSS version 26 (IBM Corp). Descriptive statistics assessed

institutional back- ground information, curricular content, and barriers. The Spearman correlation was used to measure the strength and direction of association between potential barriers that pre-vent institutions from prioritizing systemic racism in their curriculum and whether systemic racism is incorporated in the curriculum. The chi-square test was used to examine relationships between teaching systemic racism concepts and public versus private programs. The Fisher exact test was used to assess associations between traditional and accelerated programs.

RESULTS

Sixty out of 141 (42.5%) unique colleges and schools of pharmacy submitted responses to the survey; however, due to the nature of the survey, respondents were not forced to give a response for every question. In terms of baseline demographics, respondents represented by the data reflect various curricula present in the United States: nine three-year accelerated schools, 43 four-year schools, three 0 1 6-year schools, and one 2 1 4-year school. Demographic data are further presented in Table 1.

Table 1. Demographics of Respondents and Programs to Survey of Systemic Racism Education in Pharmacy Curricula

	No. (%)
Respondent title (n557)	
Administrator (dean, assistant or associate dean)	27 (47.4)
Department chair	3 (5.3)
Assessment committee chair	3 (5.3)
Curriculum committee chair	6 (10.5)
Diversity equity inclusion officer (or equivalent)	6 (10.5)
Faculty member (not otherwise specified)	9 (15.8)
Other	3 (5.3)
Institution type (n555)	
Private	29 (52.7)
Public	26 (47.3)
Program structure (n556)	
Accelerated	9 (16.1)
Traditional	47 (83.9)
Geographic region (n555)	
Northeast	8 (13.8)
Southeast	19 (32.8)
Midwest	12 (20.7)
Southwest	6 (10.3)
West	10 (17.2)

In regard to the inclusion of systemic racism content in required didactic curricula, a total of 55 responses were received to the question, "Please rate the level at which teaching about the impact that systemic racism has on health care is integrated into the curriculum at your institution." Thirteen (23.6%) respondents stated that systemic racism content was not offered at all, while 11 (20%) stated that systemic racism content was offered in one course or module. Nineteen (34.5%) respondents stated that systemic racism content was offered in more than one course or module but was not a theme across courses or modules, while four (7.3%) stated that systemic racism was a theme across multiple courses and modules. Five (9.1%) respondents stated that systemic racism was an overall theme across the curriculum and tied in with the mission of the school, while three (5.5%) stated that systemic racism was to be offered in the near future. A chi-square test revealed that the level of integration of systemic racism into curricula was not statistically different among public versus private programs, X^2 (1, $N553$)50.16, $p5.69$. Among the 42 schools indicating that systemic racism is taught within any period during the didactic year, 24 respondents said it is taught in the first year of

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pharmacy school, 22 in the second year, and 20 in the third year; this was a "select all that apply" question. Some respondents specifically noted that systemic racism is taught in a longitudinal course, elective course, advanced pharmacy practice experience (APPE), orientation, or elsewhere. Table 2 describes the systemic racism-related topics that are covered and the strategies used to teach these topics. The hours dedicated to teaching systemic racism concepts were as follows: one to five hours (15 colleges/schools of pharmacy), five to 10 hours (10 colleges/schools of pharmacy), and more than 10 hours (four colleges/schools of pharmacy), with the range being one to 25 hours.

Table 2. Didactic Systemic Racism Curricular Topics and Course Activities

Didactic activities (N541)	No. (%)
Curricular topics	
Implicit bias	33 (56.9)
Racism as a social determinant of health	31 (53.4)
Racism in health care	21 (36.2)
Microaggressions	14 (24.1)
Minority stress	11 (19.0)
Diversity, equity, and inclusion	29 (50.0)
ourse activities (strategies used) (n517)	
Cultural simulation game or activity (12.1)	7
Case studies or video case studies	15 (25.9)
Seminar series, forum, or panel discussion	7 (12.1)
Research paper or presentation	3 (5.2)
OSCE or virtual/standardized patients	7 (12.1)
Community interview of a different cultural group	3 (5.2)
Reflective writing	11 (19.0)
Role play or role-reversal exercise	7 (12.1)
Global experience	7 (12.1)
Poverty simulation	1 (1.7)

Abbreviations: OSCE5objective structured clinical examination.

For the question, "Please rate the priority at which methods to explicitly teach about systemic racism's im- pact on health and health care is prioritized in the overall curriculum at your institution," of the 57 respondents for this question, 51% indicated that this is a low priority and 32% indicated it to be an extremely low priority. Less than a quarter (17%) indicated that this is a high priority in that it receives attention at multiple levels.

According to respondents, student feedback regarding the education they receive as related to systemic racism's impact on health and health care has been mixed. For example, some students felt that it is too much information, while others expressed that the current content is insufficient. One respondent's institution took a novel approach to address student feedback by adding a diversity, equity, and inclusion question on all course evaluations.

Respondents were asked to rate the level at which teaching about the impact that systemic racism has on health care is integrated into the curriculum at their institution, and 54 completed this question. The Fisher exact test was performed to compare traditional versus accelerated programs. The analysis indicated that there is no evidence of an association between program type (accelerated vs traditional) and whether teaching on systemic racism is offered ($p5.67$). Respondents were also asked whether they requested feedback from students about incorporating systematic racism content in their curriculum. This analysis indicated that there was little evidence

for an association between program type and whether feedback from students is requested.

Regarding systemic racism content that is available outside of the didactic curriculum, of the 49 respondents that completed a question on whether learning opportunities are offered during introductory pharmacy practice experiences (IPPEs), four mentioned they are offered while 45 indicated they are not. Of the 50 respondents of a similar question on whether learning opportunities are offered during APPEs, five mentioned they are offered while 45 indicated they are not. Of the 50 respondents that completed a question on learning opportunities in cocurricular activities, 25 mentioned they offer cocurricular learning opportunities while 25 mentioned they do not.

Shifting focus to faculty involvement in teaching systemic racism, respondents were asked, "What is the level of faculty involvement in teaching or facilitating systemic racism concepts at your school?" This question was completed by 50 respondents. Most respondents (48%) re- ported that a few key faculty members (₋5%) are involved in teaching or facilitating systemic racism concepts in their curriculum. About one-third (38%) reported that a small core group of the faculty (5%-25%) is involved in teaching systemic racism concepts, 8% of respondents reported that a moderately sized group of faculty (26%- 50%) is involved in teaching systemic racism concepts, and less than 6% of respondents reported that one faculty member is involved in teaching systemic racism concepts at their institutions.

In terms of barriers to inclusion of systemic racism content in the curriculum, respondents were asked to rate each of 10 potential barriers that prevent their institutions from prioritizing systemic racism in their curriculum; 49 respondents completed this question. For each barrier, respondents used a five-point Likert scale (1 5not a barrier, 2 5minor barrier, 3 5moderate barrier, 4 5major bar- rier, and 5 5extreme barrier) to indicate the extent that each is a barrier for their institutions. More than a quarter of respondents (29%) indicated that faculty comfort level in teaching systemic racism is an extreme barrier. Nearly 20% of respondents indicated that an extreme barrier for their institutions is that there is not enough space in the curriculum, whereas 16% reported faculty knowledge and skills regarding systemic racism as an extreme barrier for their institutions. Significant correlations were identified between most barriers and whether systemic racism was incorporated into the curriculum (Table 3). Those that are significant are moderately strong correlations. Correla- tions that are negative indicate that the higher the barrier was rated by the respondent, the more likely the respondent selected the "not offered at all" response.

Lastly, when respondents were asked about their school of pharmacy's plans for curricular changes around systemic racism's impact on health and health care, 52 respondents completed this question. A majority of respondents (40%) indicated that they anticipate increasing learning opportunities within the next academic year, while 27% indicated plans to increase learning opportunities within the next five years. Ten respondents (19%) indicated that no changes are planned, while two respondents (4%) planned increased learning opportunities within the next 10 years.

DISCUSSION

To the authors' knowledge, this is the first evaluation of the inclusion of systemic racism concepts within PharmD curricula in the United States. Similar evaluations of PharmD programs focusing on health disparities, cultural competence, and health literacy have noted substantial progress in integrating these topics over the last decade.[18-20] Reviews of other health professional curricula, such as medical education, have shown variability in timing, methods, and priority of teaching social determinants of health depending on the school.[30-31] Similarly to pharmacy education, there have been calls to action and recommended frameworks to expand content beyond health disparities and cultural competence and specifically address systemic racism in medical and nursing education, but data regarding evaluation of current practices is limited.[32-34] Based on the results of this study of pharmacy curricula, there is opportunity for growth in teaching pharmacy students explicitly about systemic racism and its impact.

For most institutions that participated in this survey, the priority of teaching systemic racism concepts in the current PharmD curricula was noted as being low or extremely low. Survey results also indicate that few institutions are teaching about systemic racism as a theme across multiple courses. When included in curricula, concepts were mostly taught in the didactic portion, with few institutions addressing systemic racism during experiential rotations. This demonstrates an opportunity to integrate and build on systemic racism concepts throughout the curriculum, building through APPE rotations.

Table 3. Relationship Between Identified Barriers and Incorporation of Systemic Racism Concepts into Curricula at COP/SOP

Barrier	Spearman correlation, rho	*p* value
General resistance to curricular change	-.02	.83
Not enough space for content in curriculum	-.30	.04
Faculty lack knowledge and skills regarding systemic racism	-.05	.79
Faculty perception of existence of systemic racism	-.33	.02
Faculty comfort level teaching systemic racism	-.13	.40
Experiential roles for students do not exist for this material	-.48	.001
Faculty concern for student acceptance of material related to systemic racism	-.40	.004
Systemic racism not relevant to licensing examinations	-.32	.03
Systemic racism not included in ACPE Standards	-.36	.01

Abbreviations: COP/SOP5colleges of pharmacy/schools of pharmacy; ACPE5Accreditation Council for Pharmacy Education

A variety of teaching strategies were employed, including case studies, reflective writing, game simulations, role play exercises, standardized patients, global experiences, and seminar series/panel discussions. In the use of these strategies, it is imperative that assignments are viewed as essential components of student learning. There is a need to emphasize the importance of this content through prioritized assignments that hold weight within the curriculum. Recently, several active frameworks and pedagogical approaches have been proposed that recommend ways to interweave health equity and anti-racism education across the curriculum.[35-37] Many of these models show that curricular mapping and longitudinal integration must be instituted to ensure proper addition and sufficient education on anti-racism and health disparities in the curriculum. One proposed framework suggests an innovative five-level strategy consisting of curricular, interprofessional, institutional, community, and accreditation interventions. More specific proposed approaches include curricular integration of structural racism as a root cause of health disparities, collaboration with community policy makers and lawmakers, adoption of institutional missions directed toward social injustice, and revision of the Accreditation Standards for pharmacy education to include structural racism.[35] Another model suggests a stepwise five-phase approach by first assessing awareness through inventory measures (Phase 1), followed by elective course offerings (Phase 2), and then mandatory coursework (Phase 3). After students are exposed to initial anti-racism education, the next phase consists of curricular integration in a longitudinal manner with repeated expo- sure (Phase 4). Finally, active reflection to identify opportunities and gaps is recommended (Phase 5).[36] These frameworks may serve as a starting point for institutions to begin incorporating these concepts in an intentional and systematic manner. The addition and integration of these concepts into the curriculum should complement existing content. These concepts should be directly and longitudinally interwoven into current course offerings to prevent constraints on existing curricula.[36] There is opportunity for researchers to continue providing evidence and adding to the literature regarding practical methods and outcomes for addressing systemic racism during experiential rotations. Potential strategies include preceptor training and experiential site offerings that allow students to deepen their understanding of racial health disparities through direct patient

275 care.

According to our survey, current topics covered by institutions primarily include implicit bias, racism as a social determinant, and diversity, equity, and inclusion. While topics such as implicit bias may provide more understanding of personal prejudices, they may not address the overall impact of racism on health.[38] While an under-standing of implicit bias and cultural competency is 280 important for personal and professional development, institutions must go beyond these concepts and provide more coverage of racism as a social determinant, racism in health care, and anti-racism concepts in PharmD curricula. Respondents noted some of the major barriers to teaching systemic racism concepts were lack of faculty knowledge, skills, or comfort level, which shows there is a need for additional literature, education, and training opportunities to provide guidance. Other common 285 barriers included curricular space, relevance to the Accreditation Standards, and relevance to licensing examinations. These identified barriers further emphasize how including systemic racism content into the ACPE Standards is vital to catalyze changes in curriculum design. Although barriers vary by institution and should be addressed locally, they should be addressed by the Academy through updated Accreditation Standards that guide or direct the inclusion of systemic racism content in 290 curricula. The authors recommend that the ACPE Standards should include guidance to incorporate systemic racism education and meaningful assessment of learning outcomes intentionally and explicitly throughout the curriculum, ensuring that pharmacy students are able to identify the impact of systemic racism and how it relates to social determinants of health and health outcomes. outcomes intentionally and explicitly throughout the curriculum, ensuring that pharmacy students are 295 able to identify the impact of systemic racism and how it relates to social determinants of health and health outcomes.

There are some limitations to this work that must be considered. First, the response rate for this survey was lower than desired despite multiple reminders, representing 42.5% of pharmacy programs in the United States. However, our survey results had a distribution of colleges and schools 300 of pharmacy from across the United States, representing curricula from both public and private institutions from each geographical region. Reasons for a lower response rate could include potential survey takers were uncomfortable or unfamiliar with the topic of systemic racism, as it could be considered a sensitive subject matter. Respondents from institutions that are not currently addressing systemic racism in their curriculum may have felt the survey was not applicable. Although the 305 definition of systemic racism was provided at the beginning and throughout the survey instrument, some respondents may have interpreted the term differently. Despite the survey containing only 28 items, survey fatigue may have occurred, as many items required retrieval of information to provide an adequate response. Depending on their position and involvement within each school of pharmacy, the sur-vey taker may not have had the same knowledge as key faculty members who directly teach 310 this content. In addition, this study may not capture the "hidden curriculum," including lessons learned about racism from attitudes and behaviors modeled by faculty, preceptors, or health care staff encountered during rotations.[39] Future studies could advance the literature by triangulating data from multiple stakeholders such as students and preceptors.

315 **CONCLUSION**

Pharmacy programs in the United States appear to have integrated systemic racism education to varying degrees. Most institutions have limited coverage of these concepts, and various barriers exist to incorporating this material, namely a perceived lack of faculty knowledge, skill, and comfort level with addressing systemic racism concepts. As most institutions hope to increase learning 320 opportunities related to systemic racism in the near future, opportunities remain to expand access to training and literature to support faculty in these endeavors. Including systemic racism in clearly defined terms within the ACPE Standards could also drive meaningful change across all pharmacy curricula.

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