FACTORS AFFECTING TREATMENT OUTCOMES FOR PATIENTS UNDERGOING METHADONE TREATMENT FOR OPIOID ADDICTION
A FOCUS ON SEX HORMONES AND CHRONIC PAIN

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  - Intersection of Mental Health Perspectives & Addictions Research Training (IMPART) Fellowship; Monica Bawor & Brittany Dennis

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- All study members report no conflicts of interest, financial or otherwise.
LEARNING OBJECTIVES

1. Overview of GENOA study
2. Evaluation of sex hormones and methadone treatment
3. Impact of pain on treatment outcomes
4. Future directions for GENOA research
What is Opioid Addiction?

- DSM-V classified substance use disorder
  - Tolerance
  - Withdrawal
  - Unsuccessful effort to control
  - Impairment of social, occupational, or recreational domains
- Global prevalence: <0.8%
- Shifting demographic
- 2nd highest consumers of prescription opioids
- 200,000 opioid users

HOW IS OPIOID ADDICTION TREATED?

- Substitute opioid therapy
- Common types:
  - Methadone
  - Buprenorphine
  - Naltrexone
- 35,000 registered methadone patients
- Methadone response rates: 30-70%

Genetic influence on methadone treatment outcomes in patients undergoing methadone maintenance treatment for opioid addiction: a pilot study

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Introduction: Treatment of opioid addiction with methadone is effective; however, it is known to produce interindividual variability. This may be influenced in part by genetic variants, which can increase the initial risk of developing opioid addiction as well as explain differences in response to treatment. This pilot study aimed to assess the feasibility of conducting a full-scale genetic analysis to identify genes that predict methadone treatment outcomes in this population.

Methods: This was a cross-sectional observational study of patients admitted to a methadone maintenance treatment program for opioid addiction. We obtained demographic and clinical characteristics in addition to blood and urine samples, for the assessment of treatment outcomes.

Results: The recruitment process yielded 252 patients, representing a 20% recruitment rate. We conducted genetic testing based on a 99.6% rate of provision of DNA samples. The average retention in treatment was 3.4 years, and >50% of the participants reported psychiatric and medical comorbidities. BDNF rs6265 and DRD2 rs1799978 were the common single nucleotide polymorphisms (SNPs) selected for the feasibility study.

Discussion: This study met our predetermined feasibility criteria; recruitment, response rates,
GENETICS OF OPIOID ADDICTION (GENOA)

- Collaboration with OATC
  - Access to 55 opioid agonist therapy clinic sites across Ontario
  - Standardized treatment procedures
- Recruitment from 4 clinic sites (June-December 2011)
- Variables collected
  - Demographics
  - Anthropometric measurements
  - Substance use history
  - Medical and psychiatric history
  - Blood and urine results
OATC Potential Participants

Screen for Eligibility

Men and women
18 years or older
Able to provide consent

Eligible

Include
Baseline Visit

Consent (including access to medical records)
Interview
Methadone dose
Blood Sample

Not Eligible

Exclude if on SOT other than methadone or not willing to provide blood/urine results
SETTING & PARTICIPANTS

Figure 1 Flow diagram for participants included in the study. Abbreviation: OATC, Ontario Addiction Treatment Centres.

Samaan et al. (2014) Neuropsychiatr Dis Treat, 10
Table 1 Demographics of the GENOA study sample

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>36.9 (10.3)</td>
</tr>
<tr>
<td>Age of opioid onset in years, mean (SD)</td>
<td>23.2 (9.2)</td>
</tr>
<tr>
<td>Methadone use duration in months, mean (SD)</td>
<td>40.7 (42.6)</td>
</tr>
<tr>
<td>Methadone dose in mg/day, median (range)</td>
<td>80.0 (2–555)</td>
</tr>
<tr>
<td>Treatment response, mean (SD)</td>
<td>81.5 (23.2)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.8 (6.4)</td>
</tr>
<tr>
<td>European ethnicity, %</td>
<td>84.9</td>
</tr>
<tr>
<td>Currently married/common law, %</td>
<td>38.9</td>
</tr>
<tr>
<td>Currently employed, %</td>
<td>29.8</td>
</tr>
<tr>
<td>Current tobacco smoking, %</td>
<td>88.9</td>
</tr>
<tr>
<td>Current alcohol use, %</td>
<td>31.1</td>
</tr>
</tbody>
</table>

Samaan et al. (2014) Neuropsychiatr Dis Treat, 10
### Family history of addiction

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents, %</td>
<td>59.5</td>
</tr>
<tr>
<td>Siblings, %</td>
<td>41.3</td>
</tr>
<tr>
<td><strong>Comorbid psychiatric disorders, %</strong></td>
<td><strong>48.8</strong></td>
</tr>
<tr>
<td>Depression, %</td>
<td>32.9</td>
</tr>
<tr>
<td>Bipolar, %</td>
<td>8.7</td>
</tr>
<tr>
<td>Schizophrenia, %</td>
<td>1.6</td>
</tr>
<tr>
<td>Anxiety, %</td>
<td>27.0</td>
</tr>
<tr>
<td>Personality, %</td>
<td>4.8</td>
</tr>
<tr>
<td>Other, %</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Samaan et al. (2014) *Neuropsychiatr Dis Treat*, 10
<table>
<thead>
<tr>
<th>Comorbid medical disorders, %</th>
<th>42.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV, %</td>
<td>0.4</td>
</tr>
<tr>
<td>Hepatitis, %</td>
<td>24.2</td>
</tr>
<tr>
<td>Liver disease, %</td>
<td>6.3</td>
</tr>
<tr>
<td>Chronic pain, %</td>
<td>25.4</td>
</tr>
<tr>
<td>Epilepsy, %</td>
<td>2.0</td>
</tr>
<tr>
<td>Other, %</td>
<td>25.8</td>
</tr>
</tbody>
</table>
Past 12 months self-reported drug use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin, %</td>
<td>17.1</td>
</tr>
<tr>
<td>OxyContin, %</td>
<td>44.4</td>
</tr>
<tr>
<td>Cannabis, %</td>
<td>59.8</td>
</tr>
<tr>
<td>Stimulants, %</td>
<td>48.2</td>
</tr>
<tr>
<td>Hallucinogens, %</td>
<td>12.4</td>
</tr>
<tr>
<td>Inhalants, %</td>
<td>1.2</td>
</tr>
<tr>
<td>Performance-enhancing drugs, %</td>
<td>2.8</td>
</tr>
<tr>
<td>Barbituates, %</td>
<td>8.0</td>
</tr>
<tr>
<td>Benzodiazepines, %</td>
<td>25.5</td>
</tr>
<tr>
<td>Diet pills, %</td>
<td>2.8</td>
</tr>
</tbody>
</table>
TESTOSTERONE SUPPRESSION IN MEN AND WOMEN ON METHADONE FOR OPIOID DEPENDENCE
HOW ARE SEX HORMONES INVOLVED?

- Opioid dependence in men
- Increase in opioid use in women
- Sex differences in opioid dependence and treatment
- Sex hormones as the biological basis for sex differences
- Testosterone associated with addictive behaviors

**Research Questions**

1. What effect do opioids have on testosterone in both men and women?

2. What other methadone-related treatment factors are associated with testosterone level?

3. Does methadone suppress testosterone more than other opioids?
PARTICIPANT SAMPLE

- Measured testosterone levels in men (n=131) and women (n=100)

- Control group: Healthy adults aged 18-74 years
  - No opioid dependence

- Individuals on hormonal medications were removed from analysis
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 131)</th>
<th>Women (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years; mean (SD)</td>
<td>38.3 (11.0)</td>
<td>35.2 (9.4)</td>
</tr>
<tr>
<td>BMI; mean (SD)</td>
<td>26.9 (5.0)</td>
<td>26.6 (8.0)</td>
</tr>
<tr>
<td>Married/common law; n (%)</td>
<td>53 (40.5)</td>
<td>38 (38.0)</td>
</tr>
<tr>
<td>Employed; n (%)</td>
<td>45 (34.4)</td>
<td>25 (25.0)</td>
</tr>
<tr>
<td>Completed post-secondary education; n (%)</td>
<td>33 (25.2)</td>
<td>45 (45.0)</td>
</tr>
<tr>
<td>Age of initial opioid use in years; mean (SD)</td>
<td>23.3 (9.9)</td>
<td>23.3 (8.5)</td>
</tr>
<tr>
<td>Current cigarette smokers; n (%)</td>
<td>116 (88.5)</td>
<td>91 (91.0)</td>
</tr>
<tr>
<td>Number of cigarettes smoked/day; mean (SD)</td>
<td>17.5 (12.0)</td>
<td>14.1 (9.5)</td>
</tr>
<tr>
<td>Polysubstance use; n (%)</td>
<td>60 (45.4)</td>
<td>43 (43.0)</td>
</tr>
<tr>
<td>Psychiatric comorbidity, self-reported; n (%)</td>
<td>55 (42.0)</td>
<td>54 (54.0)</td>
</tr>
<tr>
<td>Methadone dose (mg); mean (SD)</td>
<td>90.2 (65.6)</td>
<td>83.3 (52.8)</td>
</tr>
<tr>
<td>Duration on MMT; mean (SD)</td>
<td>40.6 (38.7)</td>
<td>36.4 (45.6)</td>
</tr>
<tr>
<td>Illicit opioid use based on urine test results; mean (SD)</td>
<td>17.0 (21.3)</td>
<td>20.9 (25.6)</td>
</tr>
</tbody>
</table>

Bawor et al. (2014) Sci Rep, 4
**Effect of Opioid Use on Testosterone**

Table 2: Summary of testosterone levels between men and women on methadone and controls

<table>
<thead>
<tr>
<th></th>
<th>MMT b</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>131</td>
<td>100.10 ng/dL [72.21]</td>
</tr>
<tr>
<td></td>
<td>3.47 nmol/L [2.51]</td>
<td>2.71 nmol/L</td>
</tr>
<tr>
<td>Women</td>
<td>100</td>
<td>36.61 ng/dL [23.19]</td>
</tr>
<tr>
<td></td>
<td>1.27 nmol/L [0.81]</td>
<td>0.98 nmol/L</td>
</tr>
<tr>
<td>Total</td>
<td>231</td>
<td></td>
</tr>
</tbody>
</table>

- Significant testosterone suppression in men on methadone treatment
  - Estimated $\beta = -1.661$; 95% CI -1.793, -1.529; $p<0.0001$
- Testosterone in women on methadone was not significantly different from controls
  - Estimated $\beta = 0.063$; 95% CI -0.098, 0.224; $p=0.441$

Bawor et al. (2014) *Sci Rep*, 4
FACTORS ASSOCIATED WITH TESTOSTERONE

In men, testosterone level was associated with:

i. Methadone dose
   • Estimated $\beta = -0.003; 95\% CI -0.005, -0.001; p=0.003$

ii. Number of cigarettes smoked per day
    • Estimated $\beta = 0.011; 95\% CI 0.000, 0.021; p=0.046$
Figure 2 | Methadone dose and serum total testosterone level in men. Description: Inverse linear relationship between serum total testosterone level and methadone dose in men on methadone treatment (n = 131).
DO ALL OPIOIDS SUPPRESS TESTOSTERONE?

- Systematic review and meta-analysis

- Compared all chronic opioid users to controls
  - Any substitute opioid therapy
    - Methadone
    - Buprenorphine
  - Chronic pain relief
    - Oxycodone
  - Post-surgical pain management
    - Morphine

- Sub-group analysis based on methadone treatment
Figure 2 Forest plot of effect of opioid use on testosterone level in men
WHAT DOES THIS MEAN?

- All opioids, regardless of class or type, suppress testosterone
- Methadone does not significantly suppress testosterone any more than any other opioid
- Not enough evidence to support this finding in women
TREATMENT IMPLICATIONS

- Dose-dependent association with testosterone is present in men
- Measure testosterone levels in men prior to and during treatment
- Treat testosterone deficiency
- Men are encouraged to seek treatment with methadone
FUTURE DIRECTIONS

- Larger sample sizes
- Prospective longitudinal follow-up design
- Observing methadone outcomes after treatment of testosterone
EVALUATION OF CLINICAL AND INFLAMMATORY PROFILE IN OPIOID ADDICTION PATIENTS WITH COMORBID PAIN
PAIN IN THE METHADONE SETTING

- Pain and addiction
  - Synergistic relationship
  - Human cost of over-prescription
- Changing patient population
  - Prevalence of chronic pain (37% to 55.3%)
- Opioid-induced hyperalgesia
- Will this affect the treatment?

Does chronic pain impact response to MMT?

- Systematic review performed in duplicated across PubMED, EMBASE, Ovid (MEDLINE), and PsycINFO databases

- What did we find?
  - Sample sizes varying from 200 to 390
  - Mean age: 29.6 to 49.5 years
  - Majority male
THE BOTTOM LINE

- Limited exposure
  - Screening 500 studies across 4 databases led to retrieval of only 5 studies examining this problem

- Inconsistent findings
  - Some studies are reporting a strong association between chronic pain and continued opioid abuse among MMT patients
  - Other studies report no association

EXPLORING INCONSISTENCY IN THE MEDICAL LITERATURE

Could measurement variation explain these findings?

- Defining response to MMT
  - Percentage of positive opioid urine screens over 6 months, number of days of heroin use over the last month
  - Importance of time frame

- Measurement of response
  - Urine toxicology screening vs. self-report

- Measuring pain
  - Validated pain tool?
GENOA SAMPLE

Among patients being treated on MMT for opioid dependence, what is the clinical and inflammatory profile of patients with chronic pain?

Clinical Profile: response to MMT, demographic characteristics, physical comorbidities

Inflammatory Profile: markers of inflammation
METHODS FOR GENOA PAIN

- Data collected from 4 OATC clinics (June-December 2011)
- 235 Participants (252 recruited)
  - Reasons for exclusion
    - Concurrent opioid medication use
    - Removed outliers (dose, BMI)
    - Unwilling to provide blood sample
    - On SOT other than methadone
MEASUREMENTS

- **Chronic pain:** self-report (baseline CRF)
- **Methadone response:** measured as the % of positive opioid urine screens / the total number of urine screens
  - Urinalysis was conducted using iMDx™ Prep Assay
- **Cytokines:** determined from blood samples taken during initial enrollment
  - TNF-α, IL-1ra, IL-6, IL-8, IL-10, IFN-γ, and CCL2 serum
  - Bioplex assay (Bio-Rad Laboratories, Hercules, CA)
  - The Bioplex Manager 6.0 software was used for data analysis.
  - Cytokine measurements were expressed as pg/ml
STATISTICAL ANALYSIS METHODS

- Descriptive statistics (separated by pain status)
- Univariate analysis
- Multi-variable logistic regression model (RM)
- Model adjusted for:
  - age
  - sex
  - presence of inflammatory medications
  - presence of infectious disease
  - methadone dose (mg/day)
<table>
<thead>
<tr>
<th>Clinical and Inflammatory Profile Characteristics</th>
<th>Patients with Comorbid Pain, n=58</th>
<th>Patients without Comorbid Pain, n=117</th>
<th>P-values from Univariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic and Clinical Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>41.38</td>
<td>40.11</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean Age in Years (SD)</td>
<td>39.45 (10.29)</td>
<td>35.95 (10.26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>27.46 (5.08)</td>
<td>26.31 (5.56)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean Methadone Dose in mg/day (SD)</td>
<td>84.64 (51.51)</td>
<td>85.74 (50.14)</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean % Opioid Positive Urine Screens (SD)</td>
<td>23.99 (23.99)</td>
<td>15.82 (20.11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration on MMT in Months (SD)</td>
<td>41.31 (38.99)</td>
<td>38.25 (42.79)</td>
<td>0.61</td>
</tr>
<tr>
<td>Mean Onset Age of Opioid Abuse (SD)</td>
<td>23.21 (11.28)</td>
<td>23.16 (8.61)</td>
<td>0.98</td>
</tr>
<tr>
<td>Patients with HIV (%)</td>
<td>0.00</td>
<td>0.56</td>
<td>Unable to Determine</td>
</tr>
<tr>
<td>Patients with Hepatitis (%)</td>
<td>29.31</td>
<td>20.90</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Inflammatory Profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>1.15 (1.14)</td>
<td>1.16 (1.28)</td>
<td>0.86</td>
</tr>
<tr>
<td>IL-8</td>
<td>1.55 (0.67)</td>
<td>1.56 (0.76)</td>
<td>0.97</td>
</tr>
<tr>
<td>CCL2</td>
<td>3.25 (0.60)</td>
<td>3.14 (0.57)</td>
<td>0.26</td>
</tr>
<tr>
<td>IL-ra</td>
<td>2.96 (1.30)</td>
<td>2.96 (1.33)</td>
<td>0.92</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.35 (0.72)</td>
<td>1.30 (0.85)</td>
<td>0.62</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>2.78 (0.89)</td>
<td>2.55 (0.89)</td>
<td>0.08</td>
</tr>
<tr>
<td>TNF-α</td>
<td>2.25 (0.77)</td>
<td>2.20 (0.80)</td>
<td>0.69</td>
</tr>
</tbody>
</table>
## Table Clinical and Inflammatory Characteristics of Comorbid Pain: A Multi-variable Logistic Regression Model (n=235)

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.03</td>
<td>0.99, 1.06</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex</td>
<td>1.08</td>
<td>0.56, 2.07</td>
<td>0.82</td>
</tr>
<tr>
<td>Response to MMT (% positive opioid urine tests)</td>
<td>1.02</td>
<td>1.00, 1.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Infectious Disease Status</td>
<td>1.40</td>
<td>0.65, 3.00</td>
<td>0.38</td>
</tr>
<tr>
<td>Methadone Dose (mg/day)</td>
<td>1.00</td>
<td>0.99, 1.01</td>
<td>0.94</td>
</tr>
<tr>
<td>Presence of Inflammatory Medications</td>
<td>1.26</td>
<td>0.41, 3.92</td>
<td>0.69</td>
</tr>
<tr>
<td>TNF-Alpha</td>
<td>0.69</td>
<td>0.37, 1.30</td>
<td>0.25</td>
</tr>
<tr>
<td>IFN-Gamma</td>
<td>2.02</td>
<td>1.17, 3.50</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.18</td>
<td>0.60, 2.32</td>
<td>0.63</td>
</tr>
<tr>
<td>IL-ra</td>
<td>0.84</td>
<td>0.51, 1.37</td>
<td>0.49</td>
</tr>
<tr>
<td>CCL2</td>
<td>1.60</td>
<td>0.88, 2.88</td>
<td>0.12</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.73</td>
<td>0.43, 1.21</td>
<td>0.22</td>
</tr>
<tr>
<td>IL-10</td>
<td>1.01</td>
<td>0.69, 1.48</td>
<td>0.97</td>
</tr>
</tbody>
</table>

SUMMARY OF FINDINGS

- Patients reporting pain show higher rates of continued opioid abuse
- IFN-Gamma is slightly elevated in patients with pain
WHERE CAN WE GO FROM HERE?
FROM EXPLORATION TO CAUSATION

- External validation
- Repeated measures
- Larger sample
  - GENOA Prospective Cohort Investigation (n=311)
- Validated pain measurement
TREATMENT STRATEGIES

- How can we better manage MMT patients with comorbid pain?
  - High risk
  - Counseling, methadone case management
  - Adjunct anti-inflammatory medications
ACKNOWLEDGEMENTS

GENOA Team
Monica Bawor
Brittany B. Dennis
Carolyn Plater
Andrew Worster
Michael Varenbut
Jeff Daiter
David C. Marsh
Dipika Desai
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Lehana Thabane
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Herman Bami
Jacqueline Hudson
James Paul

McMaster University

Population Genomics Program
Impart
Gender Women Addictions

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Ontario Addiction Treatment Centres
QUESTIONS?
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