Using Wastewater Testing as a Drug Epidemiology Tool

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http://www.kingcounty.gov/environment/wtd/About/System/West.aspx
Presentation Outline

• Overview of Current Drug Abuse Indicators & Measurement limitations
• Wastewater drug testing - rationale and methods - chemistry and statistics
• Wastewater testing for drugs of abuse - examples
• Determining what drug epidemiology questions can be answered with which methods
• Q&A
Overview of Current Drug Abuse Indicator Data & Measurement Issues
What are drug epidemiology goals?

- Track changes in use over time
  - Evaluate intervention impacts
  - Changes in use or supply
- Determine level, absolute or relative, of use
  - Determine prevalence
  - Prioritize interventions
- Identify/Document new drugs
  - Identify new/incident use
  - Alert public, determine interventions
Drug Abuse Surveillance – Current Limitations

• Lack of geographic resolution - current surveys provide national-level drug use/abuse data – little at state or sub-state level
• Lack of temporal resolution (annual data) and timely availability
• Population coverage - Large portion of drug-using community currently excluded
• Small # of “events” in many jurisdictions
• Specific/actual drugs
Measurement Bias Examples

• Mortality data: only true population-level data
  – ‘Tip of the iceberg’ since mortality is biased toward more lethal drugs and lags behind entrance of drugs into ‘market’

• Current surveys usually:
  – rely on self-reporting and
  – exclude populations such as prisoners

• Drug specific ER and overdose data only for large cities

• Poison control center calls may decline as physicians recognize drug-related health problems and develop experience in treatment
Essential data comparison problem

WW is Total Population

Common data issues

- Missing highest frequency users
- Only high frequency users
- Populations being compared don’t align well
Wastewater Treatment Plant (WWTP) drug testing - Rationale and methods
Raw Wastewater Influent

- Conveniently ‘focused’ and sampled at a central location
- Least amount of degradation compared to effluent
- Preserves privacy of individuals
- Samples collected daily
- Known flows for calculation of loads

http://www.kingcounty.gov/environment/wtd/About/System/West.aspx
WWTP derived data attributes

• Cover much of the population
  – Though areas with septic not covered
• Known catchment areas
• Generally follow political boundaries
  – Aids comparisons with other data types
  – Increases utility for local planners
• GIS/Mapping data often available from local municipalities
WWTP derived data attributes

- Drug specific
- Timely- available with short lag
- Time scale-able (within day, day, month, year)
- Geographically scale-able (could aggregate municipalities or go “up-stream”)
Population covered by WWTP

WWTPs provide coverage to 85% of the population of King County, WA based upon place of residence: 1,482,427 of 1,737,034 residents
Wastewater Catchment Areas for King County Area

- Multiple places
- Moderate size
- Alignment with cities varies
Wastewater-Based Epidemiology

Venn Diagram:
- Environmental Scientists
- Wastewater Engineers
- Drug Epidemiologists

Intersection:
- Wastewater-Based Epidemiology
**SAMPLING**
- Collection mode/frequency
  - Grab
  - Composite
  - Passive
- Flow measurements
- Analyte stability
  - In-sewer transport
  - Sampling
  - Storage

**CHEMICAL ANALYSIS**
- Matrix effects
  - Use of labeled internal standards
- Analytical variability
- Calibration
  - Intra-day precision
  - Inter-day precision

**DISCHARGE BACK-CALCULATIONS**
- Pharmacokinetics
  - Metabolite choice/parent drug
  - Excretion rates
- Dose Estimates
  - Routes of administration
- Population Estimates
  - Census data
  - Biomarker tracing
  - Variation
Wastewater testing

• Types of samples
  – Grab samples
  – 24 h composite- time, volume or flow
  – Passive sampling

• Approach and frequency impact results substantially

（图）
Wastewater Collection

- Wastewater conveyance systems
  - Gravity Fed with or without Pumps stations

Locations

- Treatment plants (Downstream)
- Sewer system (Midstream)
- Building/event/single location (Upstream)
Passive Sampling

Deployed 27 days Cookville TN

Deployed 5 weeks compared to 6 hour composites taken every hour days Oslo, Norway


Portable Toilets

- **Determining Population**
  - **16 hours** of visual observation at an Interstate weigh station
  - **152 users** 93 from commercial drivers and 52 from non-commercial drivers.
  - **Commercial drivers were 64%** of the users.
Wastewater Autosamplers
Frozen and Archived Samples

- Subsample removed from composite and frozen for later analysis
Chemical Analysis

- Sample defrosted
- Isotopically labeled Internal Standard added

![Chemical structures: Amphetamine and Amphetamine-d6](Image)

- Sample preparation
  - pH adjustment
  - Filtration
  - Solid Phase Extraction (SPE)

- Quantification by tandem mass spectrometry
Standard with 12 analytes at 1.2 ng/ml

- Amphetamine
- Methamphetamine
- MDMA
- Morphine
- Acetylnorfentanyl
- Methyleone
- Naloxone
- 6-monoacetylmorphine
- Norfentanyl
- Fentanyl
- Norfentanyl
- Benzylecgonine
- Acetylnorfentanyl
- Methylone
- Cocaine
Cocaine and Heroin in Wastewater

- **Cocaine**
  - Standard: 1.2 ng/mL
  - Raw Wastewater: 290 ng/L
- **Metabolite**
  - Benzoylecgonine
    - Standard: Raw Wastewater 1120 ng/L (Saturday)
- **6-monoacetyl-morphine**
  - Raw Wastewater: < 0.002 ng/mL
- **Morphine**
  - Standard
  - Raw Wastewater: 630 ng/L

Time slightly shifted due to sample matrix
<table>
<thead>
<tr>
<th>Drug</th>
<th>Principle Metabolites</th>
<th>Percent Excreted in Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Unchanged drug</td>
<td>30–74% (^a)</td>
</tr>
<tr>
<td>Cannabinoids (THC)</td>
<td>THC–COOH, 11-OH-THC</td>
<td>Trace (^a)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Benzoylegonnine, ecdgonine methyl ester</td>
<td>1–9% (^a)</td>
</tr>
<tr>
<td>Heroin</td>
<td>Morphine, 6-acetylmorphine</td>
<td>3–50% (^a)</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Unchanged drug</td>
<td>22–76% (depending on pH) (^a)</td>
</tr>
<tr>
<td>MDA</td>
<td>Unchanged drug</td>
<td>Major component (^a)</td>
</tr>
<tr>
<td>MDEA</td>
<td>Unchanged drug</td>
<td>19% (^a)</td>
</tr>
<tr>
<td>MDMA</td>
<td>MDA</td>
<td>28% (^a)</td>
</tr>
<tr>
<td>Morphine</td>
<td>Morphine-3b-d-glucuronide</td>
<td>10% (^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75% (^a)</td>
</tr>
</tbody>
</table>
FIGURE 1.10

Number and categories of new psychoactive substances notified to the EU Early Warning System for the first time, 2009–15

Cannabinoids

Cathinones

Phenethylamines

Arylalkylamines

Tryptamines

Opioids

Benzodiazepines

Arylcyclohexylamines

Piperidines and pyrrolidines

Piperazines

Other substances
Parent Drug and Metabolite

THC(A)
Tetrahydrocannabinolic acid
On plant

THC
Psychoactive

THC-COOH
11-Nor-Δ⁹-THC-9-carboxylic acid
Metabolite
Urine ~0.6%
Feces ~3-5%
Where are these studies being conducted?

- As of 2014, Burgard et al. ES&T
- Within the next 6 months
Statistical Analyses

• Need to create:
  – Index load - estimated concentration of drug/metabolite adjusting for sample preparation procedures, total wastewater flow and population
  – Confidence bounds for estimate

• Address missing/censored data
Data from 2009 multi-city study
National Institute on Drug Abuse, R21 DA024800

• 19 cities in NW USA
• A time-based, stratified random-sampling approach accounting for seasonality and inter-week variation.
  – A total of 14 samples each quarter were obtained on random days of the week, resulting in a total of 56 samples over the course of a year per location.
• WWTP provided 24 hour composite samples.
• 6 analytes of interest:
  – BZE, methamphetamine, MDMA, oxycodone, hydrocodone, methadone
Results- Censoring

• The amount of censoring ranged from 0 to 94.2% across the (19 x 6 = 114) city-drug combinations.
• Methamphetamine exhibited the least censoring, with only Pasco having a single unobservable observation.
• At the other extreme, MDMA had complete observations for no WWTP. Censoring of MDMA observations ranged from 3.7% (Bend) to 94.2% (Hermiston), and every city had at least one observation below LOD.
• These patterns of missingness are likely related to typical usage patterns, where we might expect MDMA to be present at low quantities, if at all, on weekdays, but expect methamphetamine use to be more uniform across days of the week in the Northwest of the U.S..
The amount of censoring is indicated by the shading of the box, ranging from lightest gray to black indicating complete data.

The label underneath the WWTP names, and the background shading, indicates which method is utilized to create the estimated yearly mean below.
Figure 1: Methamphetamine index load (mg/person/day) distribution
Results

Yearly estimates with error bounds

• While the boxplots represented the distribution of observations across the year, or hypothetical distribution in the presence of censoring, in this section the final estimate of yearly average daily index load is presented.

• In addition, we focus on the error bounds created by the above combination of the error components, to give an estimate of the uncertainty around the mean.
Figure 7: Methamphetamine index load (mg/person/day) mean with 95% confidence interval
Conclusions

• Results incorporating information on all samples can be statistically analyzed and presented, results can be used to test differences between places

• The type of drug, type of place, and pattern of drug use necessarily impacts:
  – the distribution of results,
  – which impacts, statistical approaches needed to summarize the data,
  – which impacts how results can be used.
Conclusions

• For drugs and places with substantial results below detection or quantification and a desire to measure the level of drug use, citywide, 24 hour composite WWTP sampling may not yield useful results.

• Other approaches such as sampling “upstream” at a venue may be more appropriate.

• If the question is whether a drug is present or not passive sampling or “non-targeted” analysis might be appropriate.
Conclusions

• The error estimates will need to be adapted to the local context and approaches to estimating error components need to be refined e.g. population.

• Addressing censoring and error bounds is essential for producing results used for epidemiological analyses.

• Wide confidence intervals around a valid estimate are more meaningful than small CI around an invalid estimate.
Other examples of results

• SEWPROF Europe
• Student stimulant study
Spatial differences and temporal changes in illicit drug use in Europe quantified by wastewater analysis

Christoph Ort, Alexander L. N. van Nuijs, Jean-Daniel Sara Castiglioni, Adrian Covaci, Pim de Voogt, Erik Em Paul Griffiths, Félix Hernández, Iria González-Mariño, R
SEWPROF International data reporting
2015
Potential trends in Attention Deficit Hyperactivity Disorder (ADHD) drug use on a college campus: Wastewater analysis of amphetamine and ritalinic acid

Daniel A. Burgard a,*, Rick Fuller b, Brian Becker a, Rebecca Ferrell a, M.J. Dinglasan-Panlilio c

This path should correlate with times of academic stress
Significant predictors = Procrastination/Poor Time Management*, Perception of Campus Non-Rx Psychostimulant Use as Normative**
* p<0.01  **p<0.001
Recreational Cannabis
NIDA 1R03DA038806-01A1

3 Year Pilot Study of two treatment plants in Western Washington

- 8 months before recreational stores opened
- 28 months of Recreational stores
- Last 6 months state-regulated medical stores

AIMS

1. Determine the pre-retail sales levels of THC-COOH in wastewater from two WWTPs with continued analysis for the first two years.

2. Determine the correlation between measured THC-COOH levels in wastewater and national and state surveys to validate

3. Determine specific temporal (mid-week vs. weekend) variability of THC-COOH wastewater levels to describe consumption patterns

4. Estimate the contribution of the legal marketplace by comparing THC-COOH concentration levels to state sales and traceability data
Other possible applications

Questions to start with:
• What are the target analytes?
• What do they represent?
  – At the total population level
• Degradation, metabolization
• What loads are likely present?
• Chemical structure impact analysis?

Expertise needed: chemistry, toxicology, engineering, medical and public health practice, pharmacology, ethics, epidemiology...
Ethics

• Findings identify an individual/household?
  – Difficult to do, would be in law enforcement arena.

• Highlight and stigmatize a population?
  – Report findings cautiously, obscure specific location/venue/setting.

• Be careful with language- can’t ascribe motivation/behavior e.g. “abuse” to the presence of a drug
What does this mean for you?

Think carefully about:
What do you really want to know?
• Is a specific drug present?
  – In our city
  – At a specific venue?
• Comparing trends across place or time?
• What are the characteristics of the drug(s), users and system?
• Review the literature. Talk with experts.
• Consider pilot study.
  – 7-14 days
  – ~12 drugs
Questions/Discussion