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From Drug Use to Dependence: A Multiparametric Approach

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Background & Motivation

- One of the hallmarks of a drug dependence (DD) process is an escalation in rate of drug self-administration (DSA).
- We seek to extend current biostatistical approaches for epidemiological research on drug dependence processes via an investigation of a **four-parameter dose-effect curve (DEC)**.
  - **Model assumption 1**: The relationship between DD and the DSA rate (e.g., *as measured by the count of days or occasions of drug use)* exists and is "S"-shaped.
  - **Model assumption 2**: The probability of becoming drug dependent soon after onset of DSA is influenced by DSA rate, and that a feedback loop from DD to DSA rate can be ignored.
  - **Model assumption 3**: The DD is more influenced by a DSA rate than by "dose per intoxication" [9].
- The four DEC parameters help quantify potentially functional linkages that lead from DSA rate to DD.
- The response variable is the probability of becoming a case of drug dependence soon after onset of newly incident DSA; the explanatory variable is the DSA rate in the 30 days prior to an assessment date.

Methods

- We specify an 'S'-shaped increasing dose-effect curve in order to make a link from DSA rate to the fast transition probability for becoming a case of drug dependence [Pr(DD)] soon after onset of first drug use (Figure 1) [10] [1] [8] [6].
- Under this assumption, the mathematical equation relating the response to dose, x, is:

$$\Pr(DD) = \frac{\Pr_{max} - \Pr_{min}}{1 + \left(\frac{ED_{50}}{x}\right)^{k}} + \Pr_{min},$$

- $\Pr_{min}$: lower asymptote
- $\Pr_{max}$: upper asymptote
- k: Hill's coefficient
- ED_{50}: dose that is giving 50% response

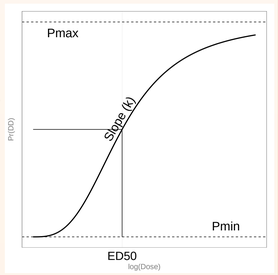


Fig. 1: The dose-effect curve corresponding to the DEC equation. The parameter values in this example are: $\Pr_{min} = 0$, $\Pr_{max} = 1$, $ED_{50} = 30$, and $k = 3$.

- A non-linear approach via a parametric function provides a straightforward and meaningful four-parameter interpretation.
- More typical epidemiological approaches do not provide the four-parameter estimation quantities used to compare each drug subtype (e.g., logistic regression [2] and other generalized linear models [3]).

Practical Implementation

- The four-parameter model can be fit using the `nls()` function, which comes with the standard R program installation [5].
- We constrained parameter values of $\Pr_{min}$ and $\Pr_{max}$ to be in the closed interval [0,1].
- We incorporated inversed empirical variances as weights to get the residuals variance structure right.
- Parameters confidence intervals were obtained by weighted residual re-sampling.

Drug Specific Dose-Effect Curves (DECs)

Materials Used For Illustration

- Data are from United States National Surveys on Drug Use and Health (NSDUH), 2002-2011, with appropriate analysis weights and Taylor series linearization variance estimates.
- Each year's NSDUH identifies newly incident drug users and DD status via confidential audio computer-administered self interviews.
- The resulting sample, drawn via multistage area probability sampling of community-dwelling US civilians age 12 years and older, is a nationally representative sample of newly incident users.
- It was possible to collect data for DEC analyses using the NSDUH "Restricted-Use Data Analysis System". [7]
- Because this work is for 'proof of concept' illustration, we do not introduce other covariates or suspected influences (e.g., male-female differences; age-of-onset variations).

DECs

- As noted, we adopt the 'dose-effect curve' (DEC) vocabulary for the purposes of illustration, with assumptions such as those stated above, to which we return in our Discussion section.
- Drug subtype by drug subtype, Figure 2 displays estimated drug-specific DECs, with empirical estimates for the probability of rapidly transitioning from first DSA to DD.

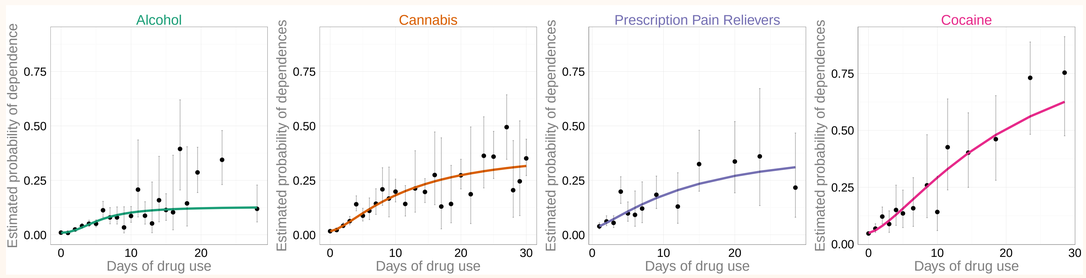


Fig. 2: Dots and vertical bars are the observed empirical estimates of drug dependence with the corresponding 95% confidence intervals. Lines are DECs – transition probabilities to drug dependence predicted by non-linear regression.

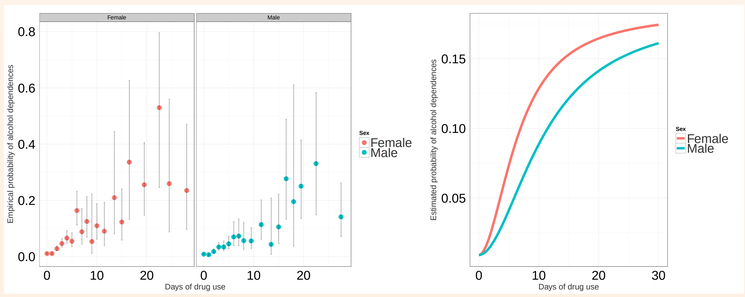
Drug	Parameters (95% Bootstrap Confidence Intervals)			
	$\Pr_{min}$	$\Pr_{max}$	ED^{*}_{50}	k
Alcohol	**0.01** (0.01, 0.01)	**0.13** (0.08, 0.27)	**6** (3, 15)	**2.16** (1.38, 4.20)
Cannabis (marijuana)	**0.02** (0.01, 0.02)	**0.39** (0.28,0.91)	**12** (7, 47)	**1.46** (1.04, 1.98)
PPR	**0.03** (0.00, 0.06)	**0.41** (0.17, 1.00)	**13** (4, 103)	**1.36** (0.71, 6.25)
Cocaine	**0.05** (0.04, 0.06)	**1.00** (0.46, 1.00)	**21** (7, 28)	**1.43** (1.18, 2.68)

Table 1: Parameter Estimates and 95% Bootstrap Confidence Intervals; * Estimated values were rounded to the nearest day.

- In terms of the four DEC parameters estimated, one might expect cocaine to have the largest estimated values of $\Pr_{min}$, $\Pr_{max}$ and ED_{50} among the drug sub-types considered, given cocaine's exceptional functional value as a reinforcer. The observed estimates are consistent with this expectation.
- By comparison, the parameter estimates for the newly incident alcohol users are dampened, but noteworthy. We offer a reminder that these estimates are based on community residents, many in adolescence and young adulthood, who had just started to drink alcohol.
- We also present estimates for prescription pain relievers (generally opioid PPR) and for cannabis, which resemble one another. We note however that the estimates for PPR are based on relatively small numbers of DSA days and small number of cases, thus have low statistical precision (i.e., very wide confidence intervals).

Female/Male Contrast for Alcohol

- To illustrate an application pertinent to women's health research, we also examined male-female variation in DECs for alcohol.
- The male and female pairs of estimates for three DEC parameters are not too distant from one another; the exception is the ED50 (7 for females and 11 for males).
- Supportive evidence for higher alcohol tolerance among men than women can be found in literature. For example, it is frequently noted that the lower ratio of water to total body weight in women causes them to metabolize alcohol and drugs differently from men [4].



Discussion

- DECs are a popular tool in other fields like pharmaceutical sciences but rarely seen in epidemiological research on drugs.
- DEC analysis allows easy differential comparison of 'S'-shaped relationships across different psychoactive drugs.
- DECs can easily be fit using existing functions in common statistical packages.
- Definitive evidence on the four-parameter DEC model will require research approaches that push beyond this initial cross-sectional evidence, but without the estimates from already available cross-sectional studies, it is impossible to lay plans for the future prospective and longitudinal research.

Limitations

- Because we are not randomly assigning the number of days of drug use, our work should be considered illustrative. Nonetheless, our methodology can be useful in prospective data analysis since it provides a clear way to differentiate between drug.
  - The current DEC estimates have the strength of nationally representative samples of newly incident drug users, but in addition to possible violations of model assumptions 1 and 2, the observed data are from point-in-time cross-sectional self-report survey assessments.
- The underlying dose-effect relationship might not be 'S'-shape in the presence of a feedback loop, i.e, soon after initial onset of drug use, an increasing pattern of repetitive days of drug use may precipitate coalescence of clinical features of DD and drive the user forward until the DD syndrome takes form. Nonetheless, once the syndrome takes form, the syndrome itself begins to drive the repetition of drug-using occasions.
  - We plan to incorporate the feedback loops in our future research.

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Conflict of Interest

Authors have no conflict of interest to declare.

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