

Validly Estimating True Dose-Response When Only Treatment versus Control is
Randomized: Principal Stratification for Causal Inference with Extended Partial
Compliance

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Abstract:

Many double-blind placebo-controlled randomized experiments with active drugs suffer from complications beyond simple noncompliance. First, the compliance with assigned dose is often partial, with patients taking only part of the assigned dose, whether active or placebo. Second, the blinding may be imperfect in the sense that there may be detectable positive or negative side-effects of the active drug, and consequently, simple compliance has to be extended to allow different compliances to active drug and placebo. Efron and Feldman (1991) presented an analysis of such a situation and discussed inference for dose-response from the non-randomized data in the active treatment arm, which stimulated active discussion, including concerning the role of the intention-to-treat principle in such studies. Here, we formulate the problem within the principal stratification framework of Frangakis and Rubin (2002), which adheres to the intention-to-treat principle, and we present a new analysis of the Efron-Feldman data within this framework. Moreover, we describe precise assumptions under which dose-response can be inferred from such non-randomized data, which seem debatable in the setting of this example. Although this article only deals in detail with the specific Efron-Feldman data, the same framework can be applied to various circumstances in both natural science and social science.