Séminaire de statistique

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Local S.36 (B37)

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Linear Structural Mean Model: Application to an on-demand study and presentation of a new diagnostic tool based on semi-parametric regression

Electronic compilation of dosing histories has revolutionized research on patient adherence to prescribed therapy (Urquhart 1997). Compared to traditional methods (pill counts, diaries,…) electronic monitoring is a more reliable assessment method (Cramer 1995) that offers more detailed and clinically relevant data on drug exposure. Every opening of the drug container is recorded over time, resulting in a time series of dosing events for each patient. These data give precise information on the variability and patterns of drug exposure within individual patients and across the patient population as a whole.

In randomized clinical trials, analyses based on the *intention to treat* (ITT) principle are commonly used to establish the efficacy of a new treatment. This approach delivers an unbiased estimate of the average effect of assigning the treatment to a patient. In the presence of variable exposure to the prescribed therapy, a more clinically relevant question is to estimate the effect of the amount of drug actually taken. Henceforth, even in a randomized trial, patients who adhere well to the assigned medication may form a selective subgroup and thus not be comparable to patients who do not adhere well. So in order to obtain unbiased estimates of the effect of assigned dose, we use a Structural Mean Model (**SMM**) (Fisher-Lapp and Goetghebeur 1999) which expresses the causal effect of a treatment as a function of the amount of drug actually taken.

In this work, we apply the linear SMM to data on patients suffering from reflux problems and who are prescribed an on-demand proton pump inhibitor (PPI) therapy (i.e. patients take the medication when they feel the need). The actual use of the on-demand

therapy in this study is driven by the severity of symptoms which varies from periods without symptoms to periods with severe symptoms. Patients were randomized between active treatment and placebo tablets. Moreover, given the large variability in treatment exposure with the on-demand regimen, it is clinically relevant to estimate the expected treatment benefit for each level of drug exposure and more specifically the maximal potential benefit corresponding to the highest recommended exposure (1 dose/day).

Finally, we investigate the assumptions of the SMM using semiparametric smoothing methods. We check whether the potential treatment free outcome under the hypothesis of no exposure shows a similar association with baseline covariates in the treatment group and in the placebo group. We model treatment free outcomes as the sum of a non-linear effect of baseline covariates, the effect of the group and a possible interaction between the group and a non-linear function of baseline covariates. Each non-linear function is modeled using a spline regression (Ruppert,Wand and Carroll 2003). The result constitutes a new formal validation tool to verify the hypothesis underlying the estimation of a linear SMM.

References:

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Urquhart, J. The electronic medication event monitor. *Clin Pharmacokinet* 1997;32 (5): 345-356.

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