

Methadone dose adjustments, plasma R-methadone levels and therapeutic outcome of opioid addiction (randomized study EudraCT : 2008-005028-10)

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Background: R/S Methadone (R/S MT) has long been used as replacement therapy in relapsing opioid dependence. However, many controversies still exist on the daily methadone doses necessary for therapy optimization. R/S MT is a 50:50 mixture of two enantiomers but R/MT accounts for the majority of its pharmacological effects. With regard to the consumption of illicit opiate, a therapeutic response of R/MT 250 ng/ml plasma concentration has been recently proposed. **Methods:** In an open-label, phase 4, randomized controlled trial involving 13 outpatient clinics in Italy, we compared two populations: the first (153 patients) with daily doses of R/S MT in order to obtain or maintain R/MT plasma concentration in a range between 80 to 250 ng/ml (experimental group), the second (155 patients) treated with daily doses of R/S MT with no control of R/MT plasma concentration (control group). The primary outcomes, assessed at 6 and 12 months, were retention in addiction treatment, reduction in illicit drug use and amelioration of social aspects as defined by the Opiate Treatment index (OTI).

Results: The linear relationship between R/S MT daily dose and plasma concentrations of the two MT enantiomers was low, thus outlining the necessity of measuring plasma R-MT levels because the dose of drug daily administered has a really poor correlation with the concentration of the active principle (R-MT) in plasma. In the 'intention to treat' statistical approach the results we obtained did not support our primary goal. In fact, a lower number of patients (81%) randomized in the experimental group remained in treatment after six months from enrollment compared to control group (91%, OR 0.42; 95%, confidence interval 0.21/0.83, $P > \chi^2$ 0.012). This difference is not present at 12 months (80% control group versus 72% experimental group, OR 0.64; 95%, confidence interval 0.38/1.09, $P > \chi^2$ 0.096). In the 'per-protocol' analysis instead, 100% of adherent patients in experimental group remained in treatment compared to 90.97% of non-adherent in control group after six months ($P > \chi^2$ 0.035) and 93.48% compared to 80% after twelve months (OR 3.58; 95%, confidence interval 0.37-1.09, $P > \chi^2$ 0.009). We observed a significant reduction trend in the intensity of abuse (Q) of heroin in both groups from the enrollment to the last interview. The reduction trend was noticed also for cocaine abuse. We recorded therefore an amelioration of the social score and so the quality of life of patients from the beginning of the study to the end. In the 'per protocol' approach the social score was better in a statistically significant way in the experimental group.

Conclusion: Although 'intention to treat' approach failed the primary outcome a subsequent 'per protocol' analysis suggested that when patients (experimental group) follows medical directions stay in treatment significantly, and both the clinical outcome and quality of life ameliorate.