Comment on “Methadone Dose Adjustments, Plasma R-Methadone Levels and Therapeutic Outcome of Heroin Users: A Randomized Clinical Trial”

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Dear Editor,

Mannaioni et al. [1], in their recent randomised clinical trial on methadone dosing adjusted according to serum R-methadone levels, chose a target window of 80–250 ng/mL R-methadone based on results by Eap et al. [2].

Eap's paper, though, clearly indicates the best threshold for therapeutic response at R-methadone levels greater than 250 ng/mL, suggesting the need for even higher levels in resistant subjects.

More recently, Meini et al. [3], also acknowledged by Mannaioni et al. [1], confirmed Eap's results, showing in their sample of methadone-treated patients the presence of a R-methadone threshold of 200 ng/mL for absence of heroin use, and

250 ng/mL for absence of craving. According to Meini's published data on graph, more than 40% of the heroin-using patients in his sample had trough R-methadone levels falling between 80 and 250 ng/mL.

Thus, it is conceivable that the target therapeutic window chosen by Mannaioni et al. [1], starting at less than one third of the optimal threshold level and ending just at it, might have been too low to deliver a clear effect in comparison with controls, both on retention in treatment and on use of illegal psychoactive substances.

It would be very interesting if the Authors could discuss further on the rationale

for their choice to use target levels much lower than those advised by Eap et al. [2] and Meini et al. [3], and known to be associated with a clinically relevant use of street heroin.

Disclosure Statement

As the sole Author, I hereby certify that I have no conflict of interests.

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References

- 1 Mannaioni G, Lanzi C, Lotti M, Galli V, Totti A, Pacileo I, Sili M, Pracucci C, Dilaghi A, Bertieri L, Quaranta M, et al: Methadone dose adjustments, plasma R-methadone levels and therapeutic outcome of heroin users: a randomized clinical trial. *Eur Addict Res* 2018; 24:9–18.
- 2 Eap CB, Bourquin M, Martin J, Spagnoli J, Livoti S, Powell K, Baumann P, Deglon J: Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. *Drug Alcohol Depend* 2000;61:47–54.
- 3 Meini M, Moncini M, Daini L, Giarratana T, Scaramelli D, Chericoni S, Stefanelli F, Rucci P: Relationship between plasma concentrations of the l-enantiomer of methadone and response to methadone maintenance treatment. *Eur J Pharmacol* 2015;760: 1–6.