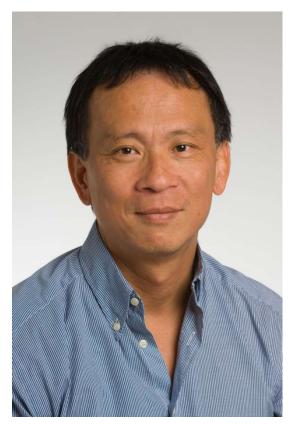


Swiss Society of Addiction Medicine Schweizerische Gesellschaft für Suchtmedizin Société Suisse de Médecine de l'Addiction Società Svizzera di Medicina delle Dipendenze

## Swiss Addiction Research Award (SARA) 2011

Prof. Dr. med. Wiesbeck President of the Curatorium

## The winners are...



PD Dr Chin B. Eap



Dr Séverine Crettol Wavre, PhD



Dr Nicolas Ansermot, PhD

Unit of Biochemistry and Clinical Psychopharmacology, Hospital of Cery, Lausanne

## Substitution of (R,S)-Methadone by (R)-Methadone

## Impact on QTc Interval

Nicolas Ansermot, PhD; Özgür Albayrak, MD; Jürg Schläpfer, MD; Séverine Crettol, PhD; Marina Croquette-Krokar, MD; Michel Bourquin, MD; Jean-Jacques Déglon, MD; Mohamed Faouzi, PhD; Norbert Scherbaum, MD; Chin B. Eap, PhD

**Background:** Methadone is administered as a chiral mixture of (*R*,*S*)-methadone. The opioid effect is mainly mediated by (*R*)-methadone, whereas (*S*)-methadone blocks the human ether-à-go-go-related gene (hERG) voltagegated potassium channel more potently, which can cause drug-induced long QT syndrome, leading to potentially lethal ventricular tachyarrhythmias.

**Methods:** To investigate whether substitution of (R,S)-methadone by (R)-methadone could reduce the corrected QT (QTc) interval, (R,S)-methadone was replaced by (R)-methadone (half-close) in 39 opioid-dependent patients receiving maintenance treatment for 14 days. (R)-methadone was then replaced by the initial close of (R,S)-methadone for 14 days (n=29). Trough (R)-methadone and (S)-methadone plasma levels and electrocardiogram measurements were taken.

**Results:** The Fridericia-corrected QT (QTcF) interval decreased when (R,S)-methadone was replaced by a half-dose of (R)-methadone; the median (interquartile range [IQR]) values were 423 (398-440) milliseconds (ms) and

412 (395-431) ms (P=.06) at days 0 and 14, respectively. Using a univariate mixed-effect linear model, the QTcF value decreased by a mean of –3.9 ms (95% confidence interval [CI], –7.7 to –0.2) per week (P=.04). The QTcF value increased when (R)-methadone was replaced by the initial dose of (R,S)-methadone for 14 days; median (IQR) values were 424 (398-436) ms and 424 (412-443) ms (P=.01) at days 14 and 28, respectively. The univariate model showed that the QTcF value increased by a mean of 4.7 ms (95% CI, 1.3-8.1) per week (P=.006).

**Conclusions:** Substitution of (*R*,*S*)-methadone by (*R*)-methadone reduces the QTc interval value. A safer cardiac profile of (*R*)-methadone is in agreement with previous in vitro and pharmacogenetic studies. If the present results are confirmed by larger studies, (*R*)-methadone should be prescribed instead of (*R*,*S*)-methadone to reduce the risk of cardiac toxic effects and sudden death.

Arch Intern Med. 2010;170(6):529-536