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Subjective and physiological responses among racemic-methadone maintenance patients in relation to relative (S)- *vs.* (R)-methadone exposure

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Aims
To investigate the possibility that (S)-methadone influences therapeutic and adverse responses to *rac*-methadone maintenance treatment, by examining how subjective and physiological responses among *rac*-methadone maintenance patients vary in relation to relative exposure to (S)- *vs.* (R)-methadone.

Methods
Mood states (Profile of Mood States), opioid withdrawal (Methadone Symptoms Checklist), physiological responses (pupil diameter, heart rate, respiration rate, blood pressure), and plasma concentrations (CP) of (R)- and (S)-methadone were measured concurrently 11–12 times over a 24-h interdosing interval in 55 methadone maintenance patients. Average steady-state plasma concentrations (C_{av}) and pharmacodynamic responses were calculated using area under the curve (AUC). Linear regression was used to determine whether variability in pharmacodynamic responses was accounted for by (S)-methadone C_{av} controlling for (R)-methadone C_{av} and *rac*-methadone dose. Ratios of (S)-:(R)-methadone using AUC_{CP} and trough values were correlated with pharmacodynamic responses for all subjects and separately for those with daily *rac*-methadone doses ≥100 mg.

Results
(S)-methadone C_{av} accounted for significant variability in pharmacodynamic responses beyond that accounted for by (R)-methadone C_{av} and *rac*-methadone dose, showing positive associations (partial *r*) with the intensity of negative mood states such as Tension (0.28), Fatigue (0.31), Confusion (0.32), and opioid withdrawal scores (0.30); an opposite pattern of relationships was evident for (R)-methadone. The plasma (S)-:(R)-methadone AUC_{CP} ratio (mean ± SD 1.05 ± 0.21, range 0.65–1.51) was not significantly related to pharmacodynamic responses for the subjects as a whole but showed significant positive associations (*r*) with the intensity of negative mood states such as Total Mood Disturbance (0.61), Tension (0.69), Fatigue (0.65), Confusion (0.64), Depression (0.49) and heart rate (0.59) for the ≥100-mg dose range.

Conclusions
These findings agree with previous evidence that (S)-methadone is associated with a significant and potentially adverse profile of responses distinct from that of (R)-methadone. Individual variability in relative (S)- *vs.* (R)-methadone exposure may be associated with variability in response to *rac*-methadone maintenance treatment.

Introduction

Methadone is a synthetic opioid commonly used as a maintenance pharmacotherapy for opioid dependence. It is normally administered orally once daily as a racemic mixture of the (R)- and (S)-methadone enantiomers. These enantiomers display different pharmacokinetic profiles [1–5], such that the ratio of each in plasma changes over a 24-h interdosing interval [4] and also varies considerably between individuals [6]. Knowledge of how variation in relative exposure to (R)- and (S)-methadone may influence the therapeutic response of patients maintained on *rac*-methadone is presently incomplete.

Methadone primarily acts on the mu (μ) opioid receptor; both enantiomers have low affinity for delta (δ) and kappa (κ) receptors [7–9]. Relative to (S)-methadone, (R)-methadone shows at least 10-fold greater affinity for the μ opioid receptor *in vitro* [7–9] and produces opioid agonist effects (e.g. analgesia, euphoria, sedation, miosis, respiratory depression) with correspondingly greater potency *in vivo* [10–12]. Although (R)-methadone is believed to account for most if not all of the therapeutic effects of methadone maintenance treatment (e.g. suppression of opioid withdrawal and cravings), *rac*-methadone is normally used due to its lower production cost and evidence that it produces similar therapeutic outcomes when compared with (R)-methadone alone [13–16].

Despite lacking strong opioid effects, (S)-methadone may be a clinically important determinant of therapeutic and adverse responses to *rac*-methadone. Administration of (S)-methadone alone in high oral doses (50–1000 mg) has been found to produce mild opioid effects (e.g. physical dependence, withdrawal suppression, respiratory depression, miosis), but is also associated with adverse subjective effects (e.g. effects disliked and described as not opioid-like) [17] and symptomatic complaints (e.g. nervousness, confusion, hallucinations) [11, 12, 17] inconsistent with μ opioid receptor activation, which may increase with chronic dosing [17]. These findings suggest that (S)-methadone may contribute significantly to the adverse but not the therapeutic effects of *rac*-methadone during maintenance treatment for opioid dependence. To this extent, treatment responses may vary between individuals as a consequence of individual variability in relative exposure to (S)- *vs.* (R)-methadone. This study investigated the possibility that (S)-methadone influences therapeutic response to *rac*-methadone maintenance treatment by examining how subjective and physiological responses among *rac*-methadone maintenance patients vary in relation to relative plasma concentrations of (S)- *vs.* (R)-methadone

Methods

Subjects

Subjects were derived from four separate investigations conducted between 1997 and 2003, two of which have been reported in part previously [18, 19] and each of which used the same subject selection criteria. For individuals who had participated in more than one of these studies, only data from the first such occasion have been included, yielding a sample size of 55. All subjects were opioid-dependent volunteers receiving methadone maintenance treatment on an outpatient basis. Inclusion criteria required subjects to be aged between 18 and 65 years and to have been maintained on once-daily oral *rac*-methadone for more than 6 weeks without a dose change in the preceding 4 weeks. Exclusion criteria included poor venous access, significant medical or psychiatric illness, elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase greater than three times the upper limit of normal range), pregnant or lactating, and the consumption of concomitant medications known to interfere with methadone pharmacokinetics (e.g. enzyme inducers, enzyme inhibitors, monoamine oxidase inhibitors). Table 1 summarizes demographic and treatment variables and urinalysis results (described below) for the subjects as a whole and separately for each study cohort (numbered chronologically according to order of commencement). The sample (all Caucasian) included subjects self-reporting both adequate ('holders', $n = 26$) and inadequate ('nonholders', $n = 29$) withdrawal suppression whilst maintained on methadone prior to commencing the study. Ethical approval to conduct these investigations was obtained

Table 1
Demographic and treatment details for 55 methadone maintenance patients as a whole and according to study cohort

Variable	Overall	Study 1	Study 2	Study 3	Study 4
N	55	18	16	12	9
Male : female (*n*)	34 : 21	11 : 7	7 : 9	10 : 2	6 : 3
Age (years)	34 ± 8	38 ± 7	36 ± 7	34 ± 9	30 ± 8
(mean ± SD, range)	(21–48)	(21–45)	(21–45)	(23–48)	(22–46)
Daily dose (mg)	80 ± 48	65 ± 34	83 ± 38	72 ± 33	113 ± 84
(mean ± SD, range)	(7.5–300)	(7.5–130)	(30–150)	(25–100)	(48–300)
Weight (kg)	73 ± 16	74 ± 11	71 ± 19	73 ± 18	74 ± 20
(mean ± SD, range)	(45–117)	(60–99)	(45–100)	(52–110)	(50–117)
Positive urinalyses (*n*)					
Opiates	14	3	6	5	0
Benzodiazepines	23	7	8	6	2
Sympathomimetic amines	5	2	1	2	0

from the Royal Adelaide Hospital Research Ethics Committee (Studies 1–3) or the University of Western Australia Human Research Ethics Committee (Study 4). All subjects provided written informed consent prior to participating.

Procedures and measures

The pharmacokinetics and pharmacodynamics of methadone were assessed over a single 24-h interdosing interval at steady-state for each subject under open-label conditions using previously described methods [19, 20]. At the beginning of each session, a urine sample was obtained for the detection of additional drug use and an intravenous cannula (18–22 G) (Becton Dickinson, Sandy, UT, USA) was inserted into a suitable forearm vein. To permit quantification of plasma (R)- and (S)-methadone concentrations, blood samples (5 ml) were obtained prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 11 and 23 h following dosing. There were two minor variations in this schedule across the four studies: (i) Study 2, a sample was collected at 12 h instead of 11 h following dosing; and (ii) Study 4, an additional 14th sample was collected at 8 h following dosing. Plasma (R)- and (S)-methadone concentrations were quantified by high-performance liquid chromatography using previously described methods [4, 21]. Precision and inaccuracies were <10% for all quality control samples (high 300 ng ml^{-1}, medium 100 ng ml^{-1}, and low 30 ng ml^{-1}) for all analytes. The concentration range of the standard curve was 15–1000 ng ml^{-1} for each enantiomer.

Pharmacodynamic responses were recorded at baseline prior to the administration of methadone and subsequently just after each blood sampling time, but no more frequently than hourly. Subjective self-report measures included:

1 Methadone Symptoms Checklist (MSC) [22]: used to record 16 withdrawal symptoms as present or absent to yield an overall measure of withdrawal severity (0–16).
2 Profile of Mood States (POMS) [23]: consists of 65 adjectives that are rated on a scale from 0 (not at all) to 4 (extremely) according to how subjects feel. These items produce scores for subscales measuring six distinct affective states (score ranges in parentheses): Tension (0–36), Anger (0–48), Depression (0–60), Vigour (0–32), Fatigue (0–28), and Confusion (0–28). High scores indicate negative affective states for all scales except Vigour; a positive mood measure. The Total Mood Disturbance scale provides a global assessment of affective state and is calculated by adding the subscales scores with Vigour weighted negatively. Total Mood Disturbance scores can range from −32 to 200 such that high scores indicate more negative mood states.

Physiological measures included:

1 Pupil diameter: measured using a video (Studies 1–3) or digital (Study 4) camera and ruler placed directly beneath the subject's eye under constant lighting conditions.
2 Respiratory rate: measured by direct observation of the subject, without their awareness, after at least 10 min of rest.
3 Heart rate: measured manually at the wrist.

4 Systolic and diastolic blood pressure: measured using a sphygmomanometer and stethoscope.

Area under the curve (AUC) was calculated (using the linear trapezoidal rule) for plasma concentrations of (R)-, (S)-, and (*rac*)-methadone, and all pharmacodynamic responses. The AUC for plasma concentrations (AUC_{CP}) and pharmacodynamic responses was divided by the duration of the study (23 h) to yield average steady-state plasma concentrations (C_{av}) and pharmacodynamic responses for each subject across the interdosing interval. As an index of the fluctuation in (S)-:(R)-plasma methadone concentration ratios within subjects during the interdosing interval, the ratio of maximum to minimum ratios for each subject was calculated. Two indices of relative exposure to (S)- and (R)-methadone were also calculated for each subject:

1 AUC_{CP} ratio: the ratio of AUC_{CP} values for (S)-:(R)-methadone concentrations was used as a measure of total relative exposure to each enantiomer across the entire dosing interval.
2 Trough ratio: since plasma samples are most often and most readily collected at the time of presentation for dosing, the plasma concentration ratio of (S)-:(R)-methadone prior to dosing (trough) was considered clinically relevant.

Statistical analyses

Since each of the four studies used the same patient selection criteria, data were combined and analysed as a single sample. Variation between studies on the demographic and treatment-related variables collected was explored using analysis of variance for continuous variables (i.e. age, dose) and χ^2 statistics for categorical variables (i.e. gender, urinalysis results), and no significant effects for study were observed. Linear regression was used to investigate relationships between average pharmacodynamic responses and (S)-methadone C_{av} controlling for (R)-methadone C_{av} and *rac*-methadone dose. The latter two predictors were entered into the equations first, followed by (S)-methadone C_{av}, in order to determine whether (S)-methadone explained significant additional variability in pharmacodynamic responses independent of (R)-methadone and total *rac*-methadone exposure. Pearson product moment correlations were used to investigate relationships between pharmacodynamic responses and indices of relative (S)- *vs.* (R)-methadone exposure. These analyses were also characterized separately for subjects with daily *rac*-methadone doses of at least 100 mg because previous studies suggest that (S)-methadone is likely to produce clinically significant effects at *rac*-methadone equivalent doses of 100 mg or more [11, 12, 17]. Partial correlations were used to determine whether relationships between relative (S)- and (R)-methadone exposures were influenced by the presence of additional drugs (listed in Table 1) in subjects' urine samples. For linear regression analyses, the assumptions of normality and homoscedascity were verified by inspection of scatter plots for the residuals. An α level of 0.05 was used for all analyses. Data are presented as mean ± SD (range) unless stated otherwise.

Results

Means for C_{av} (uncorrected for dose) during the interdosing interval for (R)-, (S)-, and *rac*-methadone were 175 ± 100 (27–493), 185 ± 117 (26–591) and 361 ± 213 (52–1067) ng ml^{-1}, respectively. Plasma concentrations for (R)-, (S)-, and *rac*-methadone ranged from 19 to 742, 21 to 1026, and 44 to 1768 ng ml^{-1}, respectively.

Linear regression analyses indicated that (S)-methadone C_{av} accounted for significant additional variance in pharmacodynamic responses beyond that accounted for by (R)-methadone C_{av} and *rac*-methadone dose (increase in R^2, *P*-value; absolute R^2) for Tension (0.08, 0.04; 0.10), Fatigue (0.09, 0.02; 0.12), and Confusion (0.10, 0.02; 0.12) and the MSC withdrawal scale (0.09, 0.03; 0.12); marginally nonsignificant results were also obtained for Total Mood Disturbance (0.06, 0.07; 0.08) and heart rate (0.07, 0.06; 0.10). Regression coefficients for each of these response variables (Table 2) indicated that (S)-methadone C_{av} was positively associated with the intensity of negative mood states, MSC withdrawal scores, and heart rate; an opposite pattern of relationships was evident for (R)-methadone C_{av}. *Rac*-methadone dose showed a similar pattern of regression coefficients to (S)-methadone C_{av} but none were statistically significant. All regression coefficients for the pharmacodynamic measures not shown in Table 2 were non-significant.

Relative plasma concentrations for (S)- *vs.* (R)-methadone concentrations showed considerable intra- and interindividual variation during the methadone interdosing interval (see examples in Figure 1). Mean fluctuation in the (S)-:(R)-methadone ratio within subjects during the interdosing interval (ratio of maximum to minimum values) was 1.50 ± 0.25 (1.15–2.31). Pharmacodynamic responses were not related to the (S)-:(R)-methadone AUC_{CP} ratio (mean 1.05 ± 0.21, 0.65–1.51) for the subject group as a whole. However, within the ≥100-mg dose range (n = 17), the (S)-:(R)-methadone AUC_{CP} ratio showed significant positive associations (r, P) with the intensity of negative mood states including Total Mood Disturbance (0.61, 0.01),

Table 2
Linear regression slope coefficients for (S)-methadone C_{av}, (R)-methadone C_{av}, and *rac*-methadone dose as predictors of average pharmacodynamic responses over a 24-h interdosing interval ($n = 55$)

	$\hat{B}$ (SE)	$\hat{\beta}$	*t*	P	Partial *r*
Total Mood Disturbance					
(S)-methadone C_{av}	0.18 (0.10)	0.68	1.82	0.07	0.25
(R)-methadone C_{av}	–0.30 (0.14)	–0.99	2.09	0.04	–0.28
Rac-methadone dose	0.24 (0.15)	0.38	1.55	0.13	0.21
Tension					
(S)-methadone C_{av}	0.04 (0.02)	0.77	2.07	0.04	0.28
(R)-methadone C_{av}	–0.06 (0.03)	–1.08	2.31	0.03	–0.31
Rac-methadone dose	0.05 (0.03)	0.42	1.73	0.09	0.24
Fatigue					
(S)-methadone C_{av}	0.05 (0.02)	0.85	2.32	0.02	0.31
(R)-methadone C_{av}	–0.08 (0.03)	–1.23	2.65	0.01	–0.35
Rac-methadone dose	0.06 (0.03)	0.46	1.91	0.06	0.26
Confusion					
(S)-methadone C_{av}	0.04 (0.01)	0.88	2.40	0.02	0.32
(R)-methadone C_{av}	–0.05 (0.02)	–1.10	2.38	0.02	–0.32
Rac-methadone dose	0.04 (0.02)	0.42	1.75	0.09	0.24
Withdrawal					
(S)-methadone C_{av}	0.02 (0.01)	0.82	2.22	0.03	0.30
(R)-methadone C_{av}	–0.03 (0.02)	–1.01	2.17	0.04	–0.29
Rac-methadone dose	0.03 (0.02)	0.43	1.79	0.08	0.24
Heart rate					
(S)-methadone C_{av}	0.05 (0.03)	0.73	1.98	0.05	0.27
(R)-methadone C_{av}	–0.08 (0.04)	–0.93	1.98	0.05	–0.27
Rac-methadone dose	0.07 (0.04)	0.41	1.70	0.10	0.23

Cav, Average steady-state plasma concentration; $\hat{B}$, estimated regression slope coefficient; SE, standard error of $\hat{B}$; $\hat{\beta}$, estimated standardized regression slope coefficient. t and P-values relate to the test of the null hypothesis that the true slope (B) is equal to zero. Partial r is the correlation between the independent and dependent variable when the linear effects of other independent variables in the model have been held fixed.

Tension (0.69, 0.002), Fatigue (0.65, 0.005), Confusion (0.64, 0.006) and Depression (0.49, 0.047), and also with heart rate (0.59, 0.01) (scatterplots for Total Mood Disturbance and Tension are shown in Figure 2). Trough plasma (S)-:(R)-methadone concentration ratios (mean 0.95 ± 0.25, 0.44–1.56) correlated strongly with AUC_{CP} ratios ($r = 0.89$, $P < 0.001$) and showed a similar pattern of relationships with pharmacodynamic responses, although statistically significant relationships (*r*, *P*) were observed only for Tension (0.53, 0.03) and Fatigue (0.52, 0.03) within the ≥100-mg dose range. Controlling for the presence of additional drugs in urine did not alter the pattern of relationships described above.

Discussion

During a 24-h interdosing interval in 55 *rac*-methadone maintenance patients (S)-methadone C_{av} accounted for significant variability in pharmacodynamic responses unaccounted for by (R)-methadone C_{av} and *rac*-methadone dose. The pattern of relationships evident for (S)-methadone C_{av} was opposite to that of (R)-methadone C_{av}, such that the former showed positive associations with the intensity of negative mood states (such as Tension, Fatigue, and Confusion) and opioid withdrawal. *Rac*-methadone dose did not account for significant variability in pharmacodynamic response independent of C_{av} for each enantiomer. Relative exposure to (S)- *vs.* (R)-methadone over the full interdosing interval, as measured by the (S)-:(R)-methadone AUC_{CP} ratio, showed significant variation across individuals (range 0.65–1.51). The (S)-:(R)-methadone AUC_{CP} ratio was not associated with pharmacodynamic responses for the subject group as a whole but was positively associated with the intensity of negative mood states and heart rate amongst higher

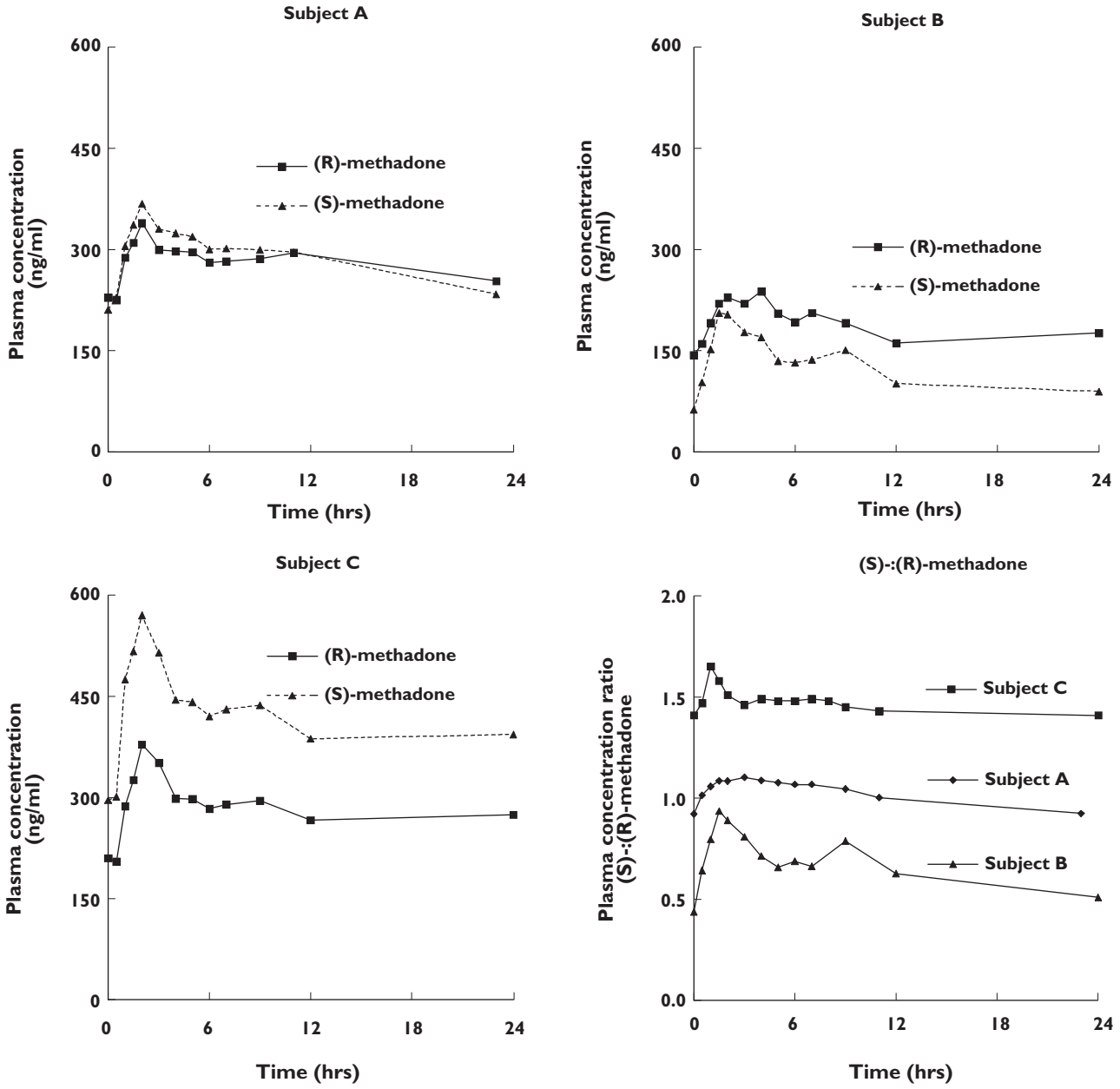

Figure 1

Plasma concentration–time profiles for (R)- and (S)-methadone during a 24-h interdosing interval in three methadone maintenance patients. Inter- and intrasubject variation in the relative plasma concentrations of (R)- and (S)-methadone are exemplified by three different subjects showing similar concentrations of each enantiomer (subject A) and relatively greater concentrations for (R)- (subject B) or (S)- (subject C) methadone. Concentrations have been normalized to a 70-mg *rac*-methadone dose. Plasma concentration ratios for (S)-:(R)-methadone are shown for each subject in the bottom right-hand panel

dose patients (100 mg or more). The ratio of (S)-:(R)-methadone at trough (i.e. the time of presentation for dosing) showed a similar pattern of results, with significant relationships evident for Tension and Fatigue, and was a strong predictor of AUC_{CP} ratios ($r = 0.89$).

The results of this study are consistent with earlier findings that (S)-methadone, particularly at higher doses (50–1000 mg), may produce an adverse profile of subjective and symptomatic effects distinct from those of (R)-methadone [11, 12, 17]. To this extent, it would be expected that the use of (R)-methadone alone instead of *rac*-methadone for maintenance treatment would yield improved treatment outcomes. Although previous comparisons of clinical efficacy and acceptability for *rac*-

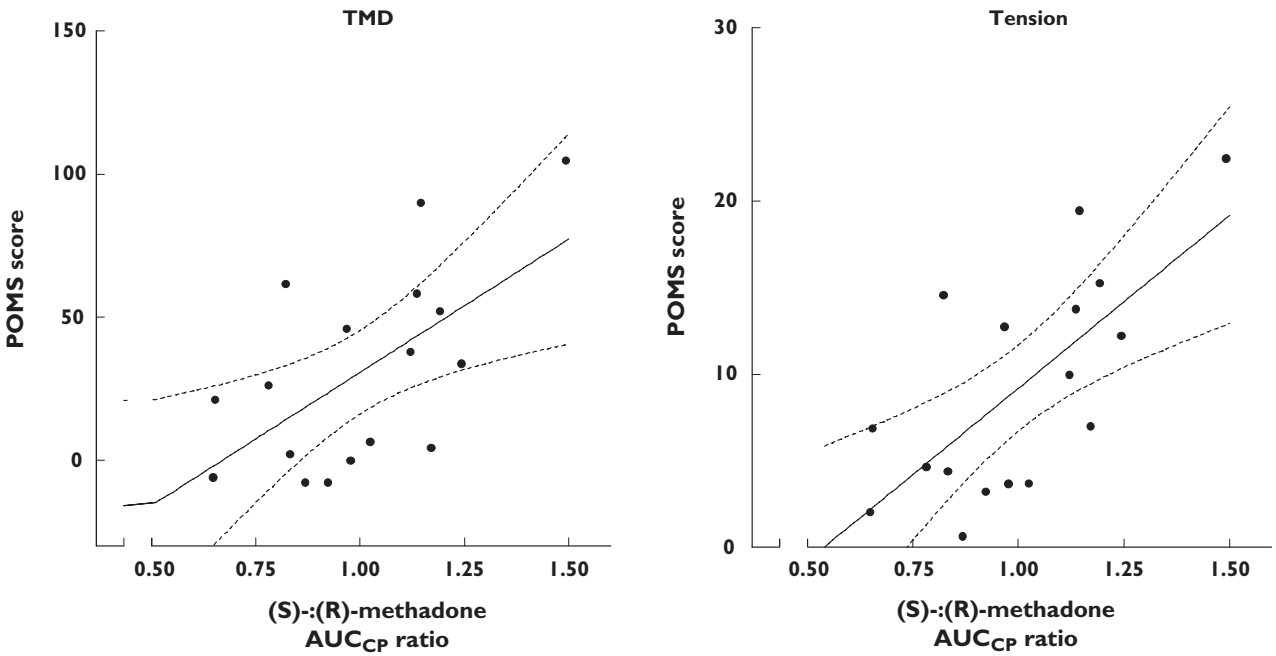

Figure 2

Relationship between the plasma AUC_{CP} ratio for (S)-:(R)-methadone and Total Mood Disturbance (TMD) ($r^2 = 0.37$, $P = 0.01$) and tension ($r^2 = 0.48$, $P = 0.002$) scores from the Profile of Mood States (POMS) during a 24-h interdosing interval in 17 patients maintained on ≥100 mg *rac*-methadone. Lines shown are the line of best fit (unbroken) and 95% confidence interval (broken) calculated using linear regression. Data represent averages for each variable calculated by dividing the area under the curve by the period of measurement (23 h)

and (R)-methadone have found no significant differences [13–16, 24], interpretation of these findings is complicated by several factors. These studies generally failed to account for variation in methadone dose or enantiomeric ratio, featured few measures of subjective effects (e.g. mood states), used small samples sizes ($n \leq 30$) [14–16, 24], and in some cases compared each formulation following a single subcutaneous injection [24] or focused only on 'substantial' symptom complaints [13]. It is also noteworthy that a significant proportion of patients (41% overall) required an increase in dose following the transfer from (R)-methadone to an equivalent *rac*-methadone dose in each of three studies for which such data were presented (10/16, 10/22 and 6/26) [14–16]. Important and potentially subtle differences in response for (R)- and *rac*-methadone may thus have been overlooked in these previous investigations.

Differences in pharmacodynamic responses for (R)- and (S)-methadone may also include effects mediated by non-opioid mechanisms [25], which could be difficult to detect using instruments designed for measurement of opioid-mediated effects. For example, both methadone enantiomers have moderate binding affinity for the NMDA receptor [26] and inhibit the neuronal reuptake of serotonin and noradrenaline [9]. Compared with (R)-methadone, (S)-methadone appears significantly less potent as an opioid agonist and inhibitor of serotonin and noradrenaline re-uptake [9]. However, both enantiomers noncompetitively inhibit the binding of NMDA receptor ligands with a potency comparable to that of the established NMDA antagonist ketamine [26], use of which has been associated with numerous adverse subjective, physiological and psychomimetic effects [27–32]. The NMDA antagonist characteristics of (S)-methadone, which are associated with significant effects in animals (e.g. antinociception, attenuation of morphine tolerance and NMDA-induced hyperalgesia) [33, 34], may contribute to adverse subjective effects in humans [17]. NMDA antagonism is also hypothesized to influence positively the analgesic efficacy [35] and level of opioid tolerance [36] associated with use of methadone for pain management. However, there remains no direct evidence for NMDA antagonist effects in humans because of the difficulty of response measurement. Other mechanisms that may hypothetically account for variation in pharmacodynamic response to racemic methadone due to variability in relative exposure to (S)- *vs.* (R)-methadone include competition between each enantiomer for binding sites on traditional opioid receptors [11] and the existence of receptor sub-

types and splice variants [37] possessing different stereoselective properties (e.g. less stereoselectivity for either enantiomer) [38]. It is also notable that methadone inhibits the activity of CYP2D6 [39, 40], CNS endogenous substrates for which may be important in regulating mood [41].

Irrespective of the mechanisms involved, the possibility that (S)-methadone produces adverse subjective and physiological responses has potential clinical implications regarding the use of *rac*-methadone for maintenance treatment in some patients. The magnitudes of these subtle effects, whilst less pronounced than the dominant opioid actions of (R)-methadone, may be important given significant variability in the plasma concentration ratio of (S)- to (R)-methadone between individuals. Therefore, in patients for whom an unfavourable profile of subjective responses to high-dose *rac*-methadone is accompanied by significantly greater exposure to (S)- *vs.* (R)-methadone, transfer to (R)-methadone alone or another alternative maintenance pharmacotherapy may be advantageous. Variability between individuals in relative exposure to (S)- *vs.* (R)-methadone and the possibility that each enantiomer produces distinct pharmacodynamic responses also highlights the importance of using stereoselective assays when monitoring plasma methadone concentrations in maintenance patients [42]. Further studies featuring administration of (R)- and (S)-methadone alone and in combination under controlled conditions, suitable for the application of advanced pharmacodynamic–pharmacokinetic modelling techniques, are needed to characterize further the importance of (S)-methadone and intra- and interindividual variability in the methadone enantiomeric ratio in relation to treatment outcomes.

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