DETERMINANTS OF OPIOID EFFECTS AND WITHDRAWAL AMONG METHADONE MAINTENANCE PATIENTS

by

Kyle R. Dyer

Department of Psychology

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Methodone maintenance is the primary effective therapy for opioid dependence. The rationale for methadone programs is to stabilise the pharmacological condition of illicit opioid users, thereby providing an opportunity to normalise health and social functioning. The extent to which this is effective for any given individual will be governed by the degree to which methadone prevents opioid withdrawal symptoms in the absence of significant direct opioid adverse effects. However, not all patients respond to methadone in the same manner, and many complain of withdrawal symptoms during the 24-hour inter-taping interval. The persistence of these complaints is a source of concern as they may signal unsanctioned drug use and poor treatment outcome. The principal aim of this thesis was to determine the factors associated with the occurrence of symptom complaints, particularly opioid withdrawal symptoms, among methadone patients.

The first study determined the frequency of symptom complaints and assessed possible patient and treatment characteristics associated with these complaints. A cross-sectional survey of 114 patients enrolled in the South Australian Public Methadone Maintenance Program was conducted, and comparisons were made with 55 age and gender matched non-opioid using controls. A checklist of 21 commonly reported symptom complaints associated with methadone maintenance treatment was administered. The methadone patients reported an average of 8 symptom complaints, with all patients reporting at least one symptom. The majority of symptoms measured were experienced by nearly one-third of the patients. The most frequently reported direct opioid effect symptoms were constipation and a dry mouth. Frequently reported opioid withdrawal symptoms were excessive sweating and muscle pain, while insomnia and reduced libido were also common. An assessment of the 7-day test re-test reliability among 38 randomly selected methadone patients indicated the consistency of these self-reports. Methadone patients also reported these symptoms to a far greater extent than non-opioid using controls. Approximately one-third of the patients reported that the methadone dose was consistently ineffective in preventing withdrawal symptoms for the
entire inter-dosing interval (i.e. the dose does not hold). These patients could not be differentiated by demographic, health, other drug use or treatment characteristics.

In the second study the temporal pattern of methadone symptom complaints during the 24-hour inter-dosing interval was assessed among 51 methadone patients. The intensity of withdrawal symptoms and direct opioid effects were measured eight times over this period. Comparisons were made between patients who reported the oral dose was 'holding' and those who did not. Many of the symptom complaints were found to vary in intensity throughout the inter-dosing interval. Direct opioid effects were maximal approximately 2-3 hours after dosing and opioid withdrawal was maximal immediately prior to dosing. Despite receiving a higher oral methadone dose, patients reporting that their daily dose did not 'hold' experienced a smaller degree of opioid effect, and a greater intensity of opioid withdrawal, during the 24-hour period. These data demonstrated that there was a change in pharmacodynamic response over the 24-hour period for all methadone patients, but that the degree of change was greater in a sub-group of patients.

In the third study, conditioned responses to opioid-related stimuli were assessed among methadone patients, in order to demonstrate classical conditioning as another potential mechanism for producing opioid withdrawal. Fifteen stabilized methadone maintenance patients were exposed to drug-related stimuli and subjective and objective responses were recorded. It was found that the intensity of subjective opioid withdrawal reported by these patients increased after presentation of a drug-related stimulus. Approximately one-half of the patients exhibited an increase of 8.00 points or more on the 48-point subjective withdrawal scale. The increase in subjective withdrawal was negatively associated with the methadone dose level, such that patients prescribed higher methadone doses exhibited smaller increments in conditioned withdrawal severity.

The time course of direct opioid effect and opioid withdrawal symptoms reported in the second study suggested a relationship with changing plasma methadone concentration during
the 24-hour inter-dosing interval. The fourth study was designed to determine plasma nociceptive methadone concentration-effect relationships for subjective and objective responses and whether pharmacokinetic and/or pharmacodynamic factors influenced withdrawal severity. Eighteen methadone patients, nine of whom experienced significant withdrawal (designated the non-holders), met the inclusion criteria of a minimum of six months enrollment and a constant methadone dose once daily for at least two months. During a single 24-hour inter-dosing interval, 13 blood samples were collected to measure plasma nociceptive methadone concentration; subjective (withdrawal severity, direct opioid effects, mood state and pain threshold) and objective (blood pressure, heart rate, respiration rate, saliva production, skin temperature, sweating and pupil size) responses were quantified on 11 occasions. The inclusion of 10 non-opioid using controls, and the absence of significant changes in subjective and objective responses among these participants, suggested that the changes recorded among the methadone patients could be reasonably interpreted as resulting from methadone ingestion. There was an inverse relationship between plasma methadone concentrations and withdrawal severity, heart rate and respiration rate, as well as a direct relationship with subjective opioid effect, pain threshold and pupil diameter. In comparison with controls, methadone patients exhibited increased anger, depression, tension, confusion and fatigue, and decreased vigour. The mood states of methadone patients were most similar to, but not equivalent with, non-opioid using controls only at peak plasma methadone concentrations. Analysis of plasma methadone concentration-effect relationships, conducted with the sigmoid E_max model, indicated that for the subjective responses, notably withdrawal severity and mood disturbance, small changes in plasma methadone concentrations translated into relatively large changes in effect. Withdrawal severity and mood disturbance were significantly associated with the rate of plasma decrease in the period from peak plasma concentrations to troughs.

When compared with methadone patients who did not report significant subjective opioid withdrawal, the non-holders exhibited a significantly shorter period of direct opioid effect and more pronounced time-dependent changes in the subjective and physiological response.
to methadone. Differences between these groups of patients were not related to oral methadone dose, other drug use, trough plasma methadone concentrations or the mean area under the plasma concentration versus time curve, but rather to the significantly more rapid hourly rate of decline in the period from the peak plasma concentration until the next dose.

Finally, a single-case study of a patient who exhibited significant opioid withdrawal despite a large trough plasma methadone concentration was conducted. Data were collected from the patient, using the same measures and procedures described above, during a once-daily dosage regimen and again during a divided dosage regimen. The reduction and division of the patient’s daily methadone dose reduced the plasma methadone concentration-time profile and thereby reduced opioid withdrawal severity and mood disturbance.

It was concluded that clinically important opioid withdrawal among methadone maintenance patients was a consequence of a more rapid rate of decline in plasma methadone concentration. The standard once-daily dosage regimen may not be suitable for a significant proportion of methadone patients. An appropriate clinical response for these patients is to shorten the inter-dosing interval. The collection of serial plasma methadone concentrations as a technique for the diagnosis and management of methadone patients who respond poorly to methadone is justified.
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