Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients

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Abstract

Background: Benzodiazepine abuse is common among methadone- and buprenorphine-maintained patients; however interactions between these drugs under high dose conditions have not been adequately examined under controlled conditions.

Objective: To investigate the effects of co-administering diazepam with methadone or buprenorphine under high dose conditions.

Design: Double-blind, randomly ordered, 2 × 2 cross-over design in which the effects of diazepam dose (0 mg versus 40 mg) and opioid dose (100% versus 150% normal dose) were examined over four sessions in methadone- and buprenorphine-maintained patients.

Participants: Four methadone- and seven buprenorphine-prescribed patients without concurrent dependence on other substances or significant medical co-morbidity.

Measures: Physiological (pulse rate, blood pressure, pupil size, respiratory rate and peripheral SpO\textsubscript{2}), subjective (ARCI, VAS ratings) and performance (reaction time, cancellation task and Digit Symbol Substitution Test, DSST) measures were taken prior to and for 6 h post-dosing.

Results: High dose diazepam was associated with time-dependent increases in the intensity of subjective drug effects (strength of drug effect, sedation) and decreases in psychological performance (reaction time, DSST) for both methadone and buprenorphine patients. These effects were generally independent of the opioid dose administered. High dose opioid administration (150% normal dose) was associated with reductions in overall SpO\textsubscript{2} levels and performance (reaction time, DSST) in the methadone patients, but had virtually no impact on pharmacodynamic responses in the buprenorphine group.

Conclusion: High dose diazepam significantly alters subjective drug responses and psychological performance in patients maintained on methadone and buprenorphine.

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Keywords: Methadone; Buprenorphine; Benzodiazepines; Diazepam; Pharmacodynamic; Interactions

1. Introduction

Methadone and buprenorphine substitution treatment have consistently been shown to be safe and effective in the treatment of heroin dependence. Nevertheless, there continue to be concerns regarding the misuse of these medications, and particularly in combination with other sedatives, such as benzodiazepines and alcohol. Such combinations have been associated with a variety of drug-related harms, including sedation, impaired motor and cognitive performance, respiratory depression and even overdose death. This paper examines pharmacodynamic responses for methadone and buprenorphine co-administered with diazepam under high dose conditions.

Benzodiazepines are widely used by heroin dependent individuals and by patients in opioid substitution treatment. Reports from methadone maintenance programs suggest that approximately one-third of patients use benzodiazepines in any given month (Ball and Ross, 1991; Darke, 1994; Stitzer et al., 1981). This high level of use may be in response to the high incidence of psychiatric co-morbidity in this population (Farre et al., 1998; Kandel et al., 2001; Marsden et al., 2000), and/or for abuse (intoxication) purposes (Stitzer et al., 1981).
A concern regarding the combination of benzodiazepines and opioids is the potential for overdose and death. Benzodiazepines have been identified in 50–80% of heroin related deaths (Grass et al., 2005; Oliver and Keen, 2003; Stenhouse and Grieve, 2003; Ward and Barry, 2001); 40–80% of methadone related deaths (Ernst et al., 2002; Mikolaenko et al., 2002; Pirnay et al., 2004; Wolf et al., 2004; Zador and Sunjic, 2000); and in up to 80% of buprenorphine related deaths (Kintz, 2001; Pirnay et al., 2004).

Given the potential for such severe adverse events, it is important to better understand the relative safety of methadone and buprenorphine when taken in combination with benzodiazepines. This may be an important factor in the selection of pharmacotherapies for opioid dependent patients. Whilst there has been some animal research comparing the effects of benzodiazepines in combination with methadone or buprenorphine (reviewed in Lintzeris et al., 2006b), there has been little human research. Earlier research by this group (Lintzeris et al., 2006b) examined the effects of single therapeutic doses of diazepam (0, 10 and 20 mg) in stable, methadone- or buprenorphine-maintained individuals without significant co-morbidity (e.g. current benzodiazepine or alcohol dependence, or taking medications known to interact with methadone, buprenorphine or diazepam). Key findings indicated that therapeutic doses of diazepam had minimal effect on physiological parameters (pulse, blood pressure, SpO2, respiratory rate), but resulted in small high doses (150% × maintenance dose) of methadone or buprenorphine. The findings of such research may be relevant in patient-treatment matching should different patterns of diazepam effects be observed in the methadone and buprenorphine patients under abuse conditions.

2. Methods

2.1. Subjects

Selection criteria were as follows: (a) aged ≥ 18 years; (b) participation in methadone or buprenorphine treatment for ≥ 4 weeks, and on stable doses for ≥ 2 weeks within the range of 30–100 mg for methadone patients, or between 4 and 6 mg for buprenorphine patients; (c) a history of benzodiazepine use, but no use within the past 2 weeks (confirmed by urine drug screen (UDS)); (d) not currently dependent on heroin, cocaine or alcohol, and able to abstain from these substances for at least 2 days prior to each session; (e) no significant medical or psychiatric condition, including severe hepatic disease (liver function tests (LFTs) more than three times greater than normal range); (f) not pregnant (confirmed by urinary βhCG); (g) no use of psychotropic medications, or other medications known to have significant interaction with either methadone, buprenorphine or diazepam. The study was conducted under conditions of voluntary informed consent with approval from the Institute of Psychiatry Human Research Ethics Committee.

2.2. Design

The study used a double-blind, randomly ordered, 2 × 2 within-subject design to investigate the effects of different doses of diazepam (0 mg or 40 mg) and the prescribed maintenance opioid (100% or 150% of daily maintenance dose) in patients maintained on methadone or buprenorphine. The four diazepam/opioid dose conditions were: (1) 0 mg diazepam + 100% maintenance dose; (2) 40 mg diazepam + 100% maintenance dose; (3) 0 mg diazepam + 150% maintenance dose and (4) 40 mg diazepam + 150% maintenance dose. Each subject participated in a total of four testing sessions (one for each drug condition), with a wash-out period of at least 4 (usually 7) days, during which serial measurements of subjective drug effects, psychomotor performance and physiological responses were made prior to, and for 6 h following drug administration. Placebo formulations of diazepam and methadone/buprenorphine were used to control for differences in the taste and volume of administered drugs in the diazepam = 0 mg and maintenance dose = 100% dose conditions. A block randomised-dosing schedule was used, with sequential allocation by the study pharmacist.

2.3. Procedures and measures

All testing sessions were conducted under controlled conditions in a room with consistent lighting and temperature. Prior to each session, subjects were screened with a urine drug screen (EMIT tests for opiates, cocaine, benzodiazepines, amphetamines) and breath alcohol reading. After baseline measures (see below), subjects were administered either their normal daily dose of methadone (10 mg/ml oral solution) or buprenorphine (sublingual 2 mg or 8 mg Subutex® tablets) in addition to a placebo (equivalent to an extra 50% of the maintenance dose), or 150% of their daily maintenance dose. Simultaneously, subjects were administered either diazepam (40 mg; 2 mg/ml) or an equivalent amount of the placebo diazepam solution. All subjects and researchers involved in data collection and analysis were blinded to dose conditions at each test session.

Physiological measures were recorded at baseline (0), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 h after dosing. Pulse rate, blood pressure (sitting) and peripheral SpO2 were measured using a Pulse Oximeter (KTMED Model KTPS-01). Pupil size and respiratory rate (over 1 min) were measured manually (using a rule and stopwatch, respectively). Subjective measures of drug effects included the Addiction Research Centre Inventory (ARCI) MBG subscale (measuring euphoria), FCAG subscale (measuring sedation) and LSD (dysphoria) (Martin et al., 1971), completed at 0, 1, 2, 3 and 5 h after dosing. Subjects also completed...
Visual Analogue Scales (0–100 mm) of ‘strength of drug effect’, ‘drug-liking’ and ‘sedation’ at 0, 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h after dosing. Performance measures were conducted at 0, 1, 3 and 5 h after dosing and included: simple visual reaction time, a measure of sensory-motor performance; cancellation of 4 s (cancellation task), a measure of focussed attention (Bond et al., 1974); the Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Scale designed to measure coding skills (Wechsler, 1955); and a balance task, a measure of the ability to maintain whole body equilibrium (Evans et al., 1987) were conducted at baseline and at 6 h to ensure subjects were not in significant opioid withdrawal, a potential confounder upon other measures. Subjects were reimbursed the equivalent of £30 in supermarket vouchers for each test session completed, and a further £30 for completing all four tests sessions.

2.4. Data analysis

Data were entered and analysed using SPSS for Windows (11.0). Pharmacodynamic responses were analysed with repeated-measures ANOVA to examine the effects of diazepam condition (placebo versus 40 mg), opioid dose condition (100% versus 150% of the daily maintenance dose), and time since dosing on all pharmacodynamic measures. These ANOVAs were conducted separately for methadone and buprenorphine. Peak effects (maximal effect compared to baseline) were analysed using paired t-tests to examine the effect of diazepam administration relative to placebo. All tests of statistical significance were two-tailed and used an alpha level of 0.05.

3. Results

3.1. Subject characteristics

Eleven subjects maintained on either methadone (n = 4) or buprenorphine (n = 7) completed all four testing sessions. The mean age (±S.D.) for the methadone and buprenorphine subjects was 39.3 ± 11.2 and 37.0 ± 10.7 years, respectively. Two methadone (50%) and six buprenorphine (86%) subjects were male. The mean daily methadone dose was 68.8 ± 21.7 mg (range 50–100 mg) daily and the mean daily buprenorphine dose was 11.1 ± 2.8 mg (range 8–16 mg). Three methadone (75%) and five buprenorphine (71%) subjects were British Caucasian, the remaining three subjects were Afro-Caribbean.

3.2. Pharmacodynamic responses

Table 1 summarises significant ANOVA effects for the diazepam and opioid dose conditions. High dose diazepam and opioid administration were associated with significant main and time-dependent effects on specific pharmacodynamic responses for both the methadone and buprenorphine groups.

3.2.1. Subjective responses. VAS ratings of strength of drug effect and sedation were significantly increased in response to high dose diazepam, with maximal levels occurring in most sessions 1–3 h following dosing, and significant diazepam and diazepam × time interaction effects observed for both methadone and buprenorphine (Table 1; Fig. 1). In contrast to the clear effects observed for ratings of strength of drug effect and sedation, ratings of drug liking showed a less pronounced and sustained increase in response to diazepam (Fig. 1), with a significant diazepam main effect in the buprenorphine group, and a diazepam × opioid dose interaction in the methadone group (Table 1). Diazepam administration was associated with greater peak subjective drug effects which reached significance on measures of sedation and strength of drug effect in the methadone group (Fig. 3). No significant effects of diazepam on peak drug effects were found in the buprenorphine group. Temporal patterns of response for the ARCI subscales (MBG, PCAG and LSD; not shown) approximated the pattern described for VAS measures; however, the former measures showed only minor

Table 1

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Diazepam</th>
<th>Diazepam × time</th>
<th>Diazepam × opioid</th>
<th>Diazepam × opioid × time</th>
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<tr>
<td></td>
<td>F</td>
<td>p</td>
<td>F</td>
<td>p</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>VAS strength</td>
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<td>0.12</td>
<td>24.2</td>
<td>0.02*</td>
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<tr>
<td>VAS liking</td>
<td>0.74</td>
<td>0.45</td>
<td>0.61</td>
<td>0.49</td>
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<tr>
<td>VAS sedation</td>
<td>3.65</td>
<td>0.15</td>
<td>51.7</td>
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<tr>
<td>SpO₂</td>
<td>24.4</td>
<td>0.02*</td>
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<td>0.21</td>
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<tr>
<td>Reaction time</td>
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<td>0.003**</td>
<td>4.38</td>
<td>0.13</td>
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<tr>
<td>DSST</td>
<td>31.7</td>
<td>0.01*</td>
<td>4.98</td>
<td>0.11</td>
</tr>
<tr>
<td>Buprenorphine</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>0.85</td>
<td>9.56</td>
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<tr>
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<td>0.56</td>
<td>18.41</td>
<td>0.005**</td>
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<tr>
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<td>6.57</td>
<td>0.04*</td>
</tr>
<tr>
<td>PCAG</td>
<td>0.08</td>
<td>0.79</td>
<td>5.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Pupil diameter</td>
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<td>0.94</td>
<td>16.14</td>
<td>0.007**</td>
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<tr>
<td>Reaction time</td>
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<td>0.16</td>
<td>8.78</td>
<td>0.03*</td>
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<tr>
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<td>0.01*</td>
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<tr>
<td>Cancellation task</td>
<td>2.35</td>
<td>0.18</td>
<td>8.37</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Pharmacodynamic responses were analysed with repeated-measures ANOVA to examine the effects of diazepam condition (0 mg vs. 40 mg), opioid dose (100% vs. 150%) and time since dosing. Only measures for which at least one significant ANOVA effect was observed are shown. There were no significant effects for opioid × time.

* \( p < 0.05 \).

** \( p < 0.01 \).
increases in response to diazepam. In general, the effects of diazepam were not significantly dependent on the opioid dose administered (100% or 150%), with only one measure showing a significant opioid dose × diazepam dose interaction term (ratings of drug liking in the methadone group, Table 1). There were no significant main effects for opioid dose on subjective measures in either the methadone or buprenorphine group (Table 1). Peak effects for subjective ratings similarly showed little effect in response to high dose opioid administration (see examples in Fig. 3).

3.2.2. Performance outcomes. Temporal patterns for performance tasks (DSST, cancellation task and reaction time) indicated that mean performance generally decreased in response to high dose diazepam for both the methadone and buprenorphine groups (Fig. 2). These performance deficits were maximal in most cases at 1 h post-dosing, with a return to baseline levels evident towards the end of the 6 h observation period. Performance measures were generally stable when the buprenorphine and methadone groups received their normal dose in the absence of diazepam, suggesting these deficits were attributable to the actions of diazepam alone and not time-dependent effects of the normal maintenance opioid dose. For the methadone group, the diazepam dose × time interaction for reaction time was the only diazepam-mediated effect on these performance measures to reach statistical significance using
Fig. 2. Performance task outcomes for reaction time, the Digit Symbol Substitution Test (DSST) and cancellation task following administration of either 0 mg diazepam (0 mg DIAZ) or 40 mg diazepam (0 mg DIAZ) in combination with either 100% or 150% of the normal maintenance opioid dose (100% OP/150% OP) of methadone (MD, \( n = 4 \)) or buprenorphine (BPN, \( n = 7 \)). Data are expressed as mean ± S.E.M.

ANOVA (Table 1). Peak effect analyses similarly indicated that high dose diazepam (alone and in combination with 150% of the opioid dose) was associated with a significant impairment on reaction time (Fig. 3). The lack of significance in peak effect analyses despite marked deterioration in performance for the cancellation task (>100%) and DSST (~40%) in the methadone group reflects a lack of statistical power due to a small sample size. For the buprenorphine group, statistical significance was achieved for (i) the main effect of diazepam on reaction time and the cancellation task and (ii) the diazepam dose \( \times \) time interaction terms for both reaction time and the DSST (Table 1). In addition, peak effect analyses indicated that high dose diazepam (alone and in combination with 150% of the opioid dose) was associated with significantly worse performance for reaction time, the DSST and the cancellation task in the buprenorphine patients (Fig. 3).

High dose opioid administration was associated with significant main effects for reaction time in the methadone group and DSST in both the methadone and buprenorphine groups (Table 1). For the methadone group, Figs. 2 and 3 indicate that the effect of high dose methadone (with either 0 mg or 40 mg diazepam) was to diminish performance on reaction time and the DSST. For the buprenorphine group, ANOVA indicated that the effect of high dose buprenorphine on DSST involved a small increase in overall performance based on comparison of estimated marginal means. However, Fig. 3 suggests the latter finding is unreliable given that scores in the high dose buprenorphine + 0 mg diazepam condition (a) were higher than scores in the control condition (100% buprenorphine dose + 0 mg diazepam condition) at baseline and (b) remained very stable following drug administration, suggesting that performance did not...
directly improve in response to buprenorphine administration.

3.2.3. Physiological responses. Unlike the subjective and performance measures, physiological parameters were not associated with any consistent pattern of effects according to the diazepam or opioid dose drug conditions. For the key safety parameter of oxygen saturation (SpO₂), the administration of 40 mg diazepam had no significant effects in either the methadone group or buprenorphine group (Table 1). Higher opioid doses had no effect on SpO₂ in the buprenorphine group. In the methadone group, higher opioid doses were associated with (1) a significant main effect involving lower overall SpO₂ levels (Table 1), and (2) a larger peak decrease in SpO₂ compared to normal opioid dose conditions, although this result was only significant in the 0 mg diazepam condition (Fig. 3). The lowest SpO₂ reading recorded in any subject was 89%, on a single occasion in a methadone subject administered 40 mg diazepam and 150% of the normal methadone dose. In 9 of the 11 subjects, SpO₂ did not fall below 93% on any occasion.

4. Discussion

This study examined the effects of high dose diazepam (0 mg versus 40 mg) and high dose opioids (100% versus 150% of daily maintenance dose) in methadone and buprenorphine maintenance patients, following an earlier study examining therapeutic doses of these drugs (Lintzeris et al., 2006b). The mean daily doses of methadone (68.8 ± 21.7 mg) and buprenorphine (11.1 ± 2.8 mg) are commonly used doses in most substitution programs within the UK and internationally. Key findings of the study indicated that (1) in both the methadone and buprenorphine
groups, high dose diazepam was associated with time-dependent increases in the intensity of subjective drug effects and changes in psychological performance; (2) these effects of diazepam were generally independent of the opioid dose administered and (3) high dose opioid administration was associated with lower SpO2 levels and psychological performance (reaction time, DSST) in the methadone group, but had no significant detrimental effects in the buprenorphine group.

These findings are clinically useful in assessing the impact that co-prescription or abuse of diazepam may have in patients undergoing opioid substitution treatment. Most changes in pharmacodynamic response peaked within 1–2 h of diazepam and opioid administration, generally reverting to baseline levels within the 6-h monitoring period. Therefore, clinical monitoring should continue for at least 2 h after the use of these medications if there are safety concerns regarding the use of benzodiazepines in conjunction with methadone or buprenorphine. The impact of the subjective and psychological performance changes associated with high dose diazepam (e.g. impaired reaction time or concentration) may be relevant to a range of activities in this population (e.g. driving skills, employment, parenting, injecting and other risk behaviour). Opioid substitution patients should be warned of the likely impact of high dose benzodiazepine use upon such activities. High dose opioid administration was also associated with significant effects on psychological performance and SpO2 in the methadone group, suggesting additional cause for concern in patients who abuse their daily prescribed daily methadone dose. These effects were generally not marked at the 150% dose condition assessed in this study, but could be clinically relevant at higher dose conditions. The mean peak reduction in peripheral SpO2 in methadone patients was approximately 3% from a baseline of 96%, with only one subject showing a SpO2 reading below the 90% level used as a clinical cut-off for defining hypoxia (Considine, 2005). The fact that administration of 150% of the maintenance dose had no significant detrimental effects in the buprenorphine group may be due to the partial agonist characteristics of buprenorphine or other factors such as opioid tolerance.

There are a number of limitations to this study that warrant caution in the conclusions that can be made. Most importantly, we have not made direct statistical comparisons of the methadone and buprenorphine groups as they are different, unmatched subjects. A definitive design for comparing these treatments would be a cross-over study in which subjects transfer between methadone and buprenorphine and are tested under different diazepam conditions whilst on each medication. This was not feasible in this study. A cross-over design would also address the fact that it is difficult to identify pharmacologically equivalent methadone and buprenorphine doses. Treatment outcome literature would suggest that the mean doses of patients in each group (methadone 69 mg versus buprenorphine 11 mg) are broadly comparable in reducing heroin use (Mattick et al., 2002), however, we can be less certain as to the pharmacological equivalence of high dose methadone and buprenorphine, partly due to the difficulties in transferring patients from one medication to another (for discussion of high dose transfers between methadone and buprenorphine see (Lintzeris et al., 2006a)). Another main limitation of the study is the small subject numbers, particularly in the methadone group. Although the within-subject design allowed for statistically significant changes to be identified, caution is required when generalising from these results to the wider population of patients in opioid substitution treatment.

Nevertheless, this is the first study of its kind to examine high dose benzodiazepine effects in buprenorphine patients alongside a group of methadone patients, and should serve as a platform for further research with larger subject numbers. Useful directions for further research include the need to consider alternative forms of benzodiazepine or opioid abuse; for example (a) individuals using much higher doses of benzodiazepines (e.g. 100 mg diazepam equivalent), (b) individuals using alternative benzodiazepines (such as shorter acting benzodiazepines such as temazepam, or those with greater anxiolytic than sedative/hypnotic effects such alprazolam) or (c) individuals misusing their methadone, buprenorphine or benzodiazepine medication by injection (Darke et al., 2002; Nielsen et al., 2005). Furthermore, there are other clinical contexts that warrant examination; in particular, interactions in methadone or buprenorphine patients maintained long-term on benzodiazepines. It is likely that tolerance would develop to many of the physiological and sedative effects of benzodiazepines with long-term use, such that any effects seen here on pharmacodynamic responses in the methadone and buprenorphine groups may be less pronounced with longer term use.

In conclusion, findings from this study indicate that benzodiazepines significantly influence response to methadone and buprenorphine, impacting upon subjective effects such as sedation, and performance effects such as attention and psychomotor skills. High dose opioid administration was also associated with significant effects including reduced oxygen saturation and psychological performance in methadone patients. Caution should be shown in the prescribing or use of high dose benzodiazepines in this population.

Conflicts of interest

Nick Lintzeris has received honoraria from Schering Plough (marketing agents for Subutex®) and Reckitt Benckiser (manufacturers of Subutex®) for facilitating educational programs regarding the use of buprenorphine. John Strang has received travel expenses and honoraria from Reckitt Benckiser and Schering Plough for attendance at meetings. Tim Mitchell, Alyson Bond and Liam Nestor have no conflicts of interest.

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Contributions: Nick Lintzeris, Alyson Bond and John Strang were responsible for designing the study and writing the protocol. Tim Mitchell, Liam Nestor and Nick Lintzeris undertook recruitment, data collection and analysis. All authors have contributed to and approved the final manuscript.

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