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Cannabis use in patients 3 months after ceasing nabiximols for the treatment of cannabis dependence: Results from a placebo-controlled randomised trial

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ABSTRACT

Introduction and Aims: Previous studies suggest cannabinoid agonist treatment is effective in reducing cannabis use in dependent treatment seekers, however few studies have reported on post-treatment outcomes. We examine cannabis use outcomes 12 weeks after cessation of treatment from a randomised placebo-controlled trial of nabiximols for the treatment of cannabis dependence.

Method: 128 participants received either nabiximols (n = 61) or placebo (n = 67) for 12 weeks, in combination with psychosocial interventions. Self-reported number of days of cannabis use in the previous 28 days was measured at baseline, 4, 8, and 12 weeks (end of treatment) and again at 24 weeks (3 months after treatment ceased). Urinalysis was used to confirm self-report data at Week 24 interview.

Results: A factorial mixed-effects model for repeated measures regression revealed that the nabiximols group used cannabis on 6.8 fewer days in the previous 28 days at week 12 (end of treatment) than the placebo group (p = 0.002, CI: 2.1,11.4), and 6.7 fewer days in the previous 28 days at the week-24 follow-up than the placebo group (p = 0.006, CI: 1.4,12.1). A significantly higher proportion of the nabiximols group (14/61; 23 %) than the placebo group (6/67; 9%) reported abstinence from cannabis in the previous 28 days at the week-24 research interview OR = 3.0, CI: 1.1, 9.1; p = 0.035, NNT = 8, CI: 4, 71).

Discussions and Conclusions: The benefits of treatment incorporating nabiximols with psychosocial interventions in reducing cannabis use appears to persist for up to 3 months after the cessation of treatment. A stepped care model of treatment is proposed.

Trial Registration: Australian New Zealand Clinical Trials Registry (ACTRN12616000103460) https://www.anzctr.org.au

1. Introduction

Cannabis accounts for the largest number of people dependent on illicit drugs globally (UNODC, 2015), and is associated with a range of adverse health effects (Volkow et al., 2014). Whilst there are no effective medications for treating cannabis dependence, there is increasing interest and evidence to support the use of cannabinoid medications for this indication (Brezing and Levin, 2017). One such medication is nabiximols, an oro-mucosal spray containing approximately equal parts of 9Δ-tetrahydrocannabinol (THC) and cannabidiol (CBD)

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extracted from cannabis plants, and licensed in many countries for the treatment of spasticity in patients with multiple sclerosis. Several clinical trials have demonstrated favourable outcomes using nabiximols to assist both short-term withdrawal management (Allsop et al., 2014), and longer term 8- and 12-week outpatient treatment integrated with psychosocial interventions (Lintzeris et al., 2019; Trigo et al., 2018). Studies also suggest the potential of synthetic Cannabinoid-1 (CB-1) agonists such as dronabinol (Budney et al., 2007; Haney et al., 2003; Levin et al., 2011) and nabilone (Haney et al., 2013) in treating cannabis use disorder.

However, studies of treatment with cannabinoid agonists have generally not reported outcomes following the cessation of treatment. In the one study that has reported post-treatment outcomes, Allsop and colleagues (2014) demonstrated nabiximols to be effective in reducing withdrawal symptoms during a brief, 6-day nabiximols inpatient withdrawal episode, however there were high (and comparable) rates of return to regular cannabis use in both placebo and nabiximols groups one month after the withdrawal episode. This suggests that brief nabiximols-assisted episodes of withdrawal management on their own are unlikely to significantly impact upon longer-term patterns of cannabis use (e.g. abstinence) – a finding consistent with the broader evidence of pharmacological interventions for the management for cannabis withdrawal (Brezing and Levin, 2017; Gorelick, 2016; Nielsen et al., 2019).

The limitations of short-term withdrawal management prompted our research group to examine a 12-week (84-day) period of nabiximols medication in combination with psychosocial interventions (Danovitch and Gorelick, 2012). Findings from our recent multisite outpatient randomised controlled trial (RCT) demonstrated significant reductions in frequency of illicit cannabis use in the nabiximols group (mean use on 35 ± 32.4 out of 84 days, 41.7 % of days) compared to the placebo group (53.1 ± 33 days, 63.1 % of days), representing 18.6 days less use (95 % CI: 3.5, 33.7) during the 12-week treatment intervention, although rates of achieving one or more 4-week periods of abstinence were not significantly different (nabiximols 26.5 % vs placebo 18.2 %). A key question we examine in this paper is whether the reduced levels of cannabis use persisted following the discontinuation of the 12-week treatment episode, or whether there were high rates of return to regular cannabis use following treatment.

This has significant clinical, regulatory and financial implications – whether we can consider the role of nabiximols-assisted treatment to be a 'short to medium' term intervention of several weeks duration to assist patients to discontinue (or at least markedly reduce) their cannabis use – as per a 'nicotine replacement' model of care, in which nicotine is combined with psychosocial interventions over a 8–12 week treatment period (Hartmann-Boyce et al., 2018; Le and Säwe, 2003). Alternatively, high rates of return to heavy cannabis use following a 12-week treatment episode would suggest the need for longer term 'maintenance' models of medication for cannabis dependence – as per methadone or buprenorphine treatment for opioid dependence.

This paper reports on cannabis use outcomes 12 weeks after the cessation of a 12-week treatment episode for cannabis dependence combining psychosocial interventions (counselling and case management) with either nabiximols or placebo.

2. Methods

2.1. Design, participants and interventions

The paper reports on findings from a double-blind randomised placebo-controlled multisite outpatient trial of nabiximols for the treatment of cannabis dependence, specifically examining cannabis use outcomes collected at 24-week research interviews, 12 weeks after the completion of the 12-week treatment phase of the study. The design and results over the 12-week treatment period of the RCT have been reported in detail elsewhere (Bhardwaj et al., 2018; Lintzeris et al., 2019).

Briefly, the study was conducted across four specialist outpatient clinics in Australia, and approved by the South East Sydney Local Health District Human Research Ethics Committee. 128 participants seeking treatment for cannabis dependence and with no other significant active comorbidities were randomly assigned to receive nabiximols or placebo, alongside psychosocial interventions (case management, cognitive behavioural therapy (CBT) based counselling), using a modified intention-to-treat analysis. Nabiximols (or placebo) was self-administered by participants using a flexible dosing schedule, with a mean dose of approximately 18 ± 9.5 sprays per day, with each spray of nabiximols delivering 2.7 mg THC and 2.5 mg CBD (equivalent to approximately 48 mg of THC and 45 mg of CBD). Similar doses of study medication were used by participants in each group. There were similar rates of attendance at CBT sessions in both groups (2.4 ± 2.2 in placebo group, 2.6 ± 2.3 in nabiximols group), and similar rates of completion of the treatment protocol (retention) at 12 weeks - 45 % in the placebo group and 49 % in the nabiximols group. The primary outcome measure, self-reported days of illicit cannabis use, was measured using a modified Timeline Follow Back technique (Sobell and Sobell, 1992) asking about the preceding 28 days at each of five research interviews: at baseline [0 weeks], 4, 8, and 12 weeks [end of treatment]) and at a 24-week follow-up interview. This paper examines cannabis use at the 24 week research interview – 12 weeks following the end of treatment. Self-reported cannabis use at week 24 was validated via urinalysis performed on samples taken at the week 24 post-treatment interview, using hydrolisation, extraction, and quantification techniques reported previously (Kevin et al., 2017; Lintzeris et al., 2019; Suraev et al., 2018). Informed consent was obtained from all participants in this study in accordance with the 1964 declaration of Helsinki.

2.2. Statistical analysis

We tested for potential differences in participant characteristics at baseline between participants who took part in the Week 24 research interview and those who did not. Differences in mean values or proportions of cases between these two groups were tested via unpaired t-tests (for categorical variables) or chi-squared tests (for categorical variables), with all values corrected for type-1 error using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995).

The primary end-point reported in this paper is frequency of cannabis use data, with two outcomes for analysis.

(i) *Days self-reported cannabis use in previous 28 days*: At each measurement point the total number of days used in the previous 28 days was recorded as a continuous outcome variable, and was analysed using a factorial mixed effects regression model for repeated measures (MMRM), with treatment (placebo vs nabiximols), time (0, 4, 8, 12, and 24 weeks) and the treatment x time interaction as the fixed factors and participant ID as the random effect. The interaction coefficients from this model, especially the group x week 24 coefficient, were the primary tests of interest as they compare group difference at each time point to group difference at baseline. Wald type-3 tests yielded omnibus effects for treatment, time, and the treatment x time interaction. All models involving multiple comparisons were corrected for type-1 error using the Benjamini-Hochberg procedure. Assumptions of regression, such as such as normality of residuals and homoscedasticity, were tested. MMRM was used to model data as it includes all cases in an analysis rather than excluding cases with missing data (Nich and Carroll, 1997), and is thought to be a more accurate method of dealing with missing data than multiple imputation (Von Hippel, 2007).

(ii) *Abstinence in preceding 28 days at Week 24*: A binary outcome variable – abstinence – was calculated from the frequency of use data, with observations of 0 days used in the previous 28 days coded as 'abstinent' and > 0 days used in the previous 28 days coded as 'non-abstinent'. Being heavy cannabis users, all

participants in the study were non-abstinent at baseline. This total absence of variance meant that the baseline abstinence data could not be used as the point of comparison against which group differences at later time points could be tested in a longitudinal logistic regression model. Therefore a different approach was taken to analysis of the abstinence data. A logistic regression was performed, regressing abstinence (abstinent vs non-abstinent) at week 24 on treatment (placebo vs nabiximols). Baseline days used in the previous 28 days (continuous) was included as a covariate in the logistic regression in order to control for any group differences in cannabis use prior to treatment commencing. Given the high rates of missing data at the 24-week research interview, we also performed the same analysis on an imputed dataset. All participants who commenced the study but had missing data at week 24 were imputed as being 'non-abstinent' (a conservative form of imputation commonly used in substance use treatment research (Haight et al., 2019)) and the logistic regression was repeated on this imputed dataset.

Self-reported cannabis use was validated using urinalysis collected at the time of the Week 24 research interview (not possible where the research interview was conducted by telephone or off-site). Receiver Operating Characteristics (ROC) curve analysis of agreement between self-reported abstinence and urinalysis estimates of abstinence were based on the criterion of creatinine-adjusted THC − COOH levels < 50 ng/mL (Baker et al., 2018).

3. Results

3.1. Participant characteristics and research follow up

Table 1 describes the key characteristics of the 128 participants recruited to the study who received one or more doses of study medication. Participants were using cannabis on 25.7 ± 4.5 days in the previous 28 days, and reported regular cannabis use for 15.7 ± 9.8 years. There were no significant differences in baseline characteristics on these measures between those who were interviewed at Week 24 (n = 55) compared to those who were not (n = 73).

Participation in research interviews at each of the five time points is shown in Table 2. Forty-three percent of participants in each group participated in the week 24 research interview (29/67 placebo; 26/61 nabiximols). Table 1 also includes the baseline characteristics of the 55 participants followed up at Week 24. Statistical analysis indicated no significant difference in baseline characteristics between those followed up (n = 55) and those not followed up at Week 24 (n = 73).

3.2. Days used in previous 28 days

Days of self-reported cannabis use in the preceding 28 days are presented in Table 2 and Fig. 1. Examination of a Quantile-Quantile plot revealed that model residuals were distributed sufficiently close to normal to support the assumptions of the MMRM. Omnibus main effects of treatment ($\chi^2(1) = 7.5$, $p = 0.006$), time ($\chi^2(4) = 219.2$, $p < 0.001$), and, importantly, the treatment x time interaction ($\chi^2(4) = 13.4$, $p = 0.009$) were all significant. Fig. 1 shows a pattern of decreasing cannabis use over the course of the 12 week trial in both groups, but with a greater rate of decrease in the nabiximols group. This pattern was confirmed by the comparisons within the MMRM. When controlling for all other time points and for multiple comparisons, the nabiximols group had used significantly fewer days in the previous 28-day period compared to baseline at both the end of treatment (week-12 interview) and at the week-24 follow-up interview: an estimated 6.5 fewer days in the previous 28-day period at week 12 ($p = 0.006$, 95 %CI: -11.7, -1.4) and an estimated 6.1 fewer days in the previous 28-day period at week 24 ($p = 0.018$, 95 %CI: -11.8, -0.4).

3.3. Abstinence at week 24

Abstinence rates in each treatment group at each timepoint during the trial and at the week 24 follow-up are shown in Fig. 1b. (solid lines and shapes for the complete case analysis and dotted lines for the imputed dataset).Twenty of the 55 participants (36.4 %) who completed the week 24 follow-up interview reported total abstinence for the previous 28 days, 14/26 (53.8 %) in the nabiximols group and 6/29 (20.7 %) in the placebo group. In comparison, at week 12 18 % (7/38) of the placebo group reported abstinence in the previous 28 days and 27 % in the nabiximols group. The logistic regression revealed a significant group difference in odds of abstinence at week 24 when controlling for days used at baseline (Odds Ratio = 4.5, 95 %CI: 1.4, 16.2, $p = 0.014$), with a Numbers Needed to Treat of 3 (95 % CI = 2, 11). In the imputed dataset (assigning worse-case scenario where missing data assigned as 'non-abstinent') the proportions abstinent in both groups dropped (nabiximols 14/61 (23.0 %), placebo 6/67 (9.0 %)), nevertheless the group difference remained significant (Odds Ratio = 3.0; 95 % CI: 1.1, 9.1; $p = 0.035$, NNT of 8 (3.8–70.3).

Table 1
Participant characteristics at baseline for participants who did not supply data at week 24 and for participants who did supply data at week 24.

	Participants Who Did Not Supply Data at Week 24			Participants Who Supplied Data at Week 24			
	Placebo(n=38)	Nabiximols(n = 35)	Total(n = 73)	Placebo(n = 29)	Nabiximols(n = 26)	Total(n = 55)	p^a
Demographic Variables							
Age, mean (SD), y*	33.2 (9.9)	32.9 (11.5)	33.1 (10.1)	34.6 (10.9)	40.5 (11.6)	37.4 (11.5)	0.24
Female sex, No. (%)	7 (18.4)	9 (25.7)	16 (21.9)	7 (24.1)	7 (26.9)	14 (25.4)	0.67
Born in Australia, No. (%)	33 (86.8)	30 (85.7)	63 (86.3)	23 (79.3)	21 (80.8)	44 (80.0)	0.67
Aboriginal/Torres Strait Islander, No. (%)	3 (7.9)	3 (8.6)	6 (8.2)	3 (10.3)	1 (3.9)	4 (7.7)	1.00
Tertiary educated, No. (%)	12 (31.6)	17 (48.6)	29 (39.7)	10 (34.5)	10 (38.5)	20 (36.4)	0.99
Employment as Main Source of Income, No. (%)	21 (55.3)	23 (65.7)	44 (60.3)	15 (51.7)	12 (46.2)	27 (49.1)	0.67
In a relationship, No. (%)	15 (39.5)	10 (28.6)	25 (34.2)	12 (41.4)	8 (30.8)	20 (36.4)	1.00
Have ≥ 1 Child, No. (%)	14 (36.8)	7 (20.0)	21 (28.8)	9 (31.0)	14 (53.8)	23 (41.8)	0.57
Current Legal Problems, No. (%)	5 (13.2)	1 (2.9)	6 (8.2)	1 (3.5)	1 (3.9)	2 (3.6)	0.67
Cannabis Use Variables							
Number of days used in last 28, mean (SD)*	26.3 (4.5)	25.6 (5.0)	26.0 (4.7)	24.7 (4.5)	26.2 (4.0)	25.4 (4.3)	0.67
Average grams per day used, mean (SD)*	2.8 (2.2)	2.1 (1.4)	2.4 (2.2)	2.4 (2.3)	2.0 (1.3)	2.2 (1.9)	0.67
Duration Since First Use, mean (SD)*	18.8 (9.5)	16.4 (10.2)	17.7 (9.8)	18.8 (9.7)	24.6 (11.2)	21.6 (10.7)	0.24
Duration Since First regular Use, mean (SD); yrs*	15.6 (9.2)	12.4 (7.6)	14.1 (8.6)	15.1 (9.4)	20.1 (10.5)	17.5 (10.2)	0.24

a: p-value tests difference, averaged across treatment, between participants who provided data at the week 24 research interview and participants who did not: *t*-test for continuous variables (marked with asterisk) and chi-squared test for categorical variables. All p-values corrected for multiple comparisons using the Benjamini-Hochberg procedure for controlling the false discovery rate.

Table 2
Between-group differences in days of cannabis use in the previous 28-day period during the 12-week Trial and at week 24 follow-up.

	Week 0		Week 4		Week 8		Week 12		Week 24	
	P M (SD)	N M (SD)	P M (SD)	N M (SD)	P M (SD)	N M (SD)	P M (SD)	N M (SD)	P M (SD)	N M (SD)
N	67	61	55	49	43	35	38	37	29	26
Days Used[a]	25.6 (4.5)	25.9 (4.6)	19.3 (10.2)	16.0 (11.3)	16.6 (11.6)	12.1 (11.8)	18.0 (11.1)	10.9 (11.0)	14.1 (11.6)	7.5 (11.0)
Difference[b] **(95% CI)**	0.2 (-4.0, 4.4)		−3.5 (-8.1, 1.0)		−4.1(-9.2, 1.0)		−6.5** (-11.7, -1.4)		−6.1* (-10.8, -3.1)	

*p < 0.05, **p < 0.01, ***p < 0.001. Significant interaction effects in bold. P = Placebo, N = Nabiximols. a: values represent number of days used in the previous 28 days. b: Estimated difference between Nabiximols and Placebo groups in days used in the previous 28 days at the time point in question. Negative estimates indicate Nabiximols group scored lower than Placebo. p-values and confidence intervals corrected for multiple comparisons using the Benjamini-Hochberg procedure.

3.4. Validation of self-report

Thirty-three of the 55 (60 %) participants who completed Week 24 interview also provided a urine sample at week 24, with similar proportions in each group (35 % Placebo, 46 % Nabiximols). In 91 % (30/33) of observations there was agreement between self-reported abstinence (0 days used vs > 0 days used) and urinalysis (THC − COOH < 50 ng/mL vs THC − COOH ≥ 50 ng/mL). The three observations where there was a discrepancy between self-reported and urinalysis occurred because participants reported low frequency cannabis use (1 or 2 days used in previous 28 days, and therefore 'non-abstinent'), and their THC − COOH levels were negative (below the 50 ng/mL cut-off) for cannabis use. These analyses corroborate participant self-report regarding recent cannabis use.

4. Discussion

These findings suggest that the additional benefit that nabiximols provides in reducing cannabis use during treatment is maintained up to 3 months after treatment has ceased. Previous research examining cannabinoid agonist treatment of cannabis dependence had either not reported outcomes following cessation of medication (Levin et al., 2011, 2016; Trigo et al., 2018), or had demonstrated that nabiximols treatment during brief inpatient withdrawal episodes did not significantly impact upon longer term cannabis use compared to placebo (Allsop et al., 2014). Our findings indicate that a more prolonged period of treatment with nabiximols appears to have been more successful in achieving sustained reductions in cannabis use, persisting beyond the cessation of treatment.

Our previous inpatient withdrawal study (Allsop et al., 2014) was conducted in the same geographical areas in Australia, recruited patients with comparable histories of cannabis use and related co-morbidities, and used similar daily doses of nabiximols. This suggests that the different outcomes seen between the studies following cessation of treatment are likely due to differences in the treatment models rather than individual patient, social or cultural factors that can hinder comparisons between studies. In this regard, the longer duration of medication and the combination with psychosocial interventions (as opposed to a brief inpatient withdrawal episode) appear to be important factors in achieving the enhanced longer-term outcomes. Another factor may be the treatment setting itself. Research from alcohol (Nadkarni et al., 2017) and opioid (Day and Strang, 2011) treatment suggests that whilst inpatient treatment settings are often associated with higher rates of treatment completion, outpatient treatment approaches require patients to make behavioural changes whilst in their usual social environments, which is often more sustainable following treatment cessation.

Our findings indicate that the treatment model – involving a time-limited period of cannabinoid agonist (nabiximols) treatment combined with case management and CBT-based counselling – is effective in reducing cannabis use for up to 12 weeks after cessation of treatment, in terms of both the average number of days of cannabis use by participants and the proportion of individuals meeting criteria for abstinence. This suggests that a treatment paradigm similar to time-limited nicotine replacement therapy may be feasible for many people seeking treatment for their cannabis dependence.

This is in contrast to the prevailing model for opioid agonist treatment – historically referred to as 'maintenance' treatment. The original model of methadone treatment for heroin dependence developed by Dole and Nyswander (1965) proposed a long term treatment requiring many years of therapy. Subsequent attempts at short-term opioid agonist treatment (e.g. weeks to months) repeatedly demonstrated high rates of return to regular use following treatment discontinuation (Amato et al., 2013), with evidence supporting enhanced outcomes following opioid agonist treatment of at least 2 years duration (Kimber et al., 2015).

The implications of our findings are considerable. Had we observed high rates of return to heavy cannabis use following the discontinuation of medication – it would suggest long-term medication may be required to sustain positive treatment outcomes –with significant implications for the cost and burden of treatment for patients, treatment providers and funders. However, our findings suggest that a short-to medium term period of treatment of between 8–12 weeks (most reductions in cannabis use were reported by week 8 in most patients) may be sufficient to assist many, though not all, patients in making the behavioural changes required to discontinue or significantly reduce their cannabis use longer term. In this regard – our treatment paradigm is more consistent with a 'nicotine replacement' model of therapy, where medication is used to assist to manage withdrawal, reduce cravings and change behavioural patterns of tobacco use, without the need for long-term medication in most cases (Hartmann-Boyce et al., 2018; Le and Säwe, 2003).

There are two major study limitations that require highlighting. The main concern is the poor research follow-up rate at 24 weeks – with only 43 % of the 128 participants completing research interviews. Although the follow up rates were comparable for both groups, there is the possibility that participants lost to follow up had poorer outcomes, limiting the significance of our findings. We have attempted to address the low follow-up data by imputing for missing data – using MMRM approaches for continuous 'days used' data, and assigning 'worse case' scenario for the categorical 'abstinence' outcome at Week 24. Nevertheless the low follow-up rate requires caution in the interpretation of our findings, and highlights the need for replication studies. The other main limitation is the relative short duration of follow-up (12 weeks). Dependence is a relapsing remitting chronic condition, and longer term follow up (e.g. 12 months) is ideally required.

Despite these limitations, our findings suggest that a 'stepped care' model of treatment using nabiximols can be considered. Many people with cannabis dependence are able to successfully discontinue cannabis use without seeking formal treatment. Others find psychosocial counselling approaches to be effective, particularly for those with less severe levels of cannabis use disorder (Chatters et al., 2016; Sabioni and Le Foll, 2019). Nabiximols treatment – in combination with psychosocial interventions should be reserved for those who are unable to curtail

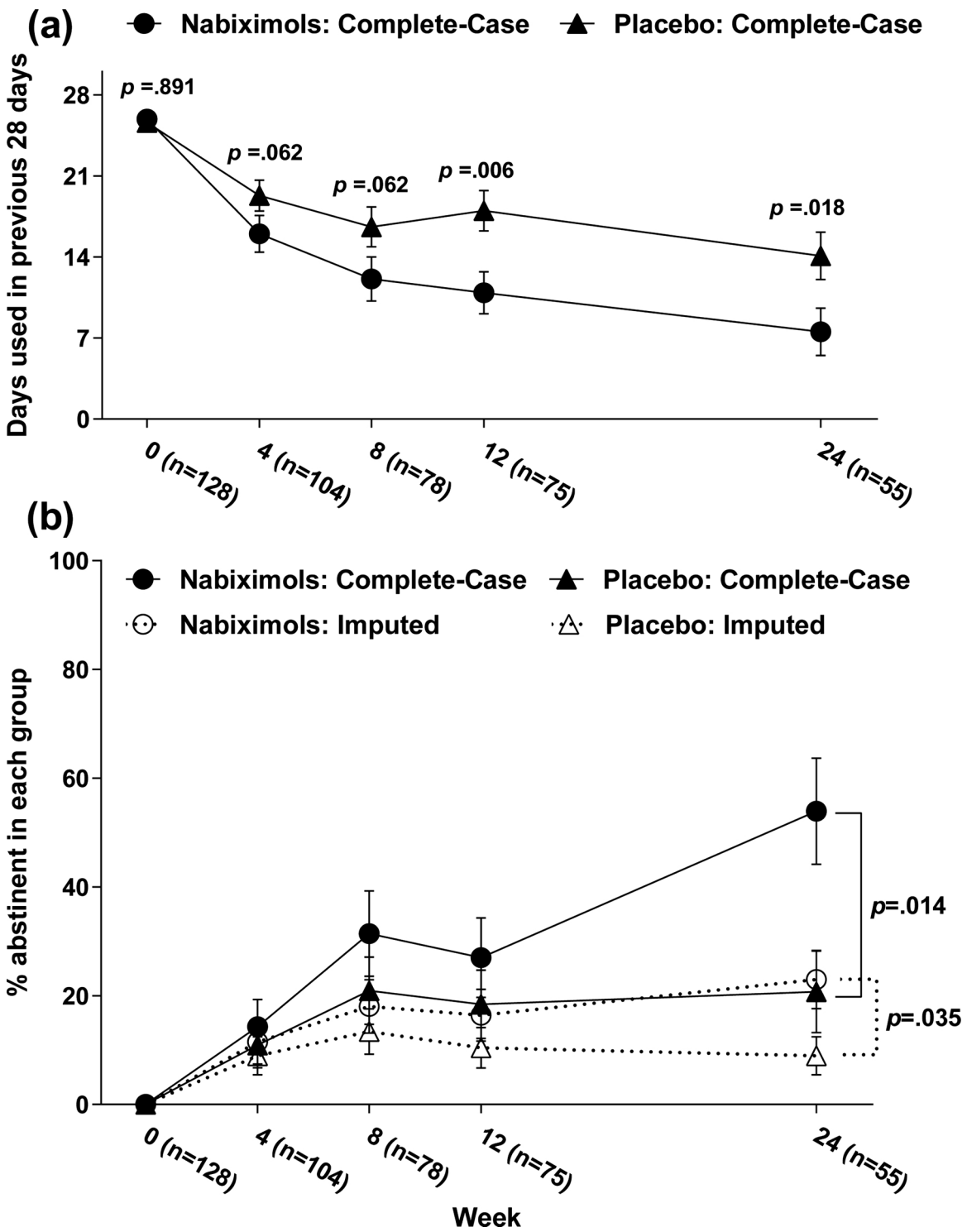

Fig. 1. Group differences in (a) days used at each time point and (b) proportion of participants who were abstinent at each time point.
Note: Error bars in (a) refer to standard error, error bars in (b) are standard error of a proportion $\sqrt{\frac{p(1-p)}{n}}$

their cannabis use with psychosocial interventions alone, initially using a time limited 8 to 12 week duration of medication. Our findings suggests that ongoing nabiximols treatment beyond this time frame may not be necessary for many patients, and should possibly be reserved for those patients who demonstrate benefit by being able to reduce their cannabis use during treatment with nabiximols, but who return to heavy cannabis use following nabiximols discontinuation. Such a stepped care approach would target medication to those most likely to require and to benefit from this approach. Further research is required to examine this approach.

4.1. Conclusions

Treatment combining nabiximols with psychosocial interventions can be effective in assisting cannabis dependent patients to reduce their cannabis use, with benefits persisting beyond the discontinuation of medication. This provides an exciting and novel approach for treating cannabis dependence, the most prevalent type of drug dependence -

following alcohol and tobacco, in the world.

5. Author contributions

Manuscript composed by Nick Lintzeris and Llewellyn Mills. Llewellyn Mills performed all data analysis. All remaining named authors assisted with editing and proofing the manuscript. The Agonist Replacement for Cannabis Dependence (ARCD) study group members are Raelene Dojcinovic, Betty Jago, Lynsey McKendrick, Consuelo Rivas, Ricardo Schwanz, Abigail Yang, and Zachary Zavareh, all from South Eastern Sydney Local Health District; Susan Hazelwood, Josephine Hindson, Melissa Jackson, Julian Keats, Craig Sadler, and Anthony Winmill, all from Hunter New England Local Health District; Angelo Barbaro, Kerin Black, Pip Bowden, Jonathon Coreas, Tim Ho, Shyam Nagubandi, Mahsa Shahidi, Catherine Silsbury, Lisa Snell, and Matthew Wijanto, all from Western Sydney Local Health District. Members of this group assisted with patient consultation, data collection, and data entry.

Contributors

Concept and design: Lintzeris, Dunlop, Copeland, McGregor, Bruno, Montebello, Bhardwaj.

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Statistical analysis: Lintzeris, Mills, Bruno, Kirby.

Obtained funding: Lintzeris, Dunlop, Copeland, McGregor, Montebello.

Administrative, technical, or material support: McGregor, Kevin, Hall, Jefferies, Bhardwaj

Supervision: Lintzeris, Bhardwaj, Dunlop.

The role of the funding source

The study was an investigator-led trial with the University of Sydney as the study sponsor. The NHMRC grant supported research costs; health services were predominately funded by the participating NSW Health services, and study medications (nabiximols, placebo) were provided free by GW Pharmaceuticals. The sponsor and funding bodies had no direct involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor decision to submit the manuscript for publication.

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The study was an investigator-led trial with the University of Sydney as the study sponsor. National Health and Medical Research Council project grant 1,088,902 supported research costs, health services were predominantly funded by the participating New South Wales health services, and study medications were provided free by GW Pharmaceuticals.

Declaration of Competing Interest

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