Treatment Outcomes of Methamphetamine Dependent Clients Prescribed Modafinil

Dr Dan Wilson

Drug and Alcohol Services South Australia (DASSA)

SA Health

October 2019

Government of South Australia
SA Health

DRUG & ALCOHOL SERVICES SOUTH AUSTRALIA

Table of Contents

Research Aim

Presented is a retrospective, observational case series of patients prescribed modafinil for methamphetamine dependence during outpatient treatment at an Australian, community-based drug and alcohol treatment service. This study aims to describe the demographic and substance use characteristics of this patient group, and to measure continuous treatment engagement at monthly time-points over 3 months.

The primary outcome measure of this study is continuous retention in treatment at 1-, 2- and 3-month time-points following commencement of modafinil. This study will assess for associations between participant characteristics and longer continuous treatment engagement (specifically, continuous treatment retention to 3 months).

A secondary aim of the study is to inform future research frameworks for this population, including analysis/clinical audit of the described service's modafinil protocol from a quality use of medicines perspective.

Literature review

Methamphetamine use is a significant public health concern in Australia, and is associated with a broad range of psychological, medical and social problems [(1)]. Data from the 2016 National Drug Strategy Household Survey (NDSHS) showed that 1.4% of Australians over the age of 14 had used methamphetamine in the past 12 months [(2)]. While there has been a reduction in the number of Australians reporting methamphetamine use in the previous 12 months since the 2013 NDSHS, it is noted that the overall burden of harm related to methamphetamine use in Australian is increasing [(1,3)]. This is likely to relate to changes in the pattern of methamphetamine use in Australia. The proportion of people using crystalline methamphetamine – a more potent form – is increasing, the number of people smoking or injecting methamphetamine as their primary method of use is increasing, and the frequency of use for people using methamphetamine is increasing [(1,3)]. These changes are likely to be driving the increasing prevalence of methamphetamine dependence among regular users.

Methamphetamine use increases extracellular monoamine levels in the brain by stimulating release and blocking pre-synaptic re-uptake. Increased synaptic dopamine levels in the mesocorticolimbic system are regarded as central to the rewarding and reinforcing effects of Methamphetamine [(4, 5)]. Regular methamphetamine use results in structural and metabolic neuroadaptation within the central nervous system, which can cause tolerance, dependence, craving and withdrawal [(6)], and promote continuing use and difficulty with attempts at cessation. Methamphetamine-dependent individuals also demonstrate cognitive deficits in a range of domains including learning, memory, attention and impulse control, which may relate to neuroadaptation and to neuronal damage resulting from methamphetamine exposure [(4, 5)].

Methamphetamine withdrawal is typically protracted, lasting for weeks to months and causing hypersomnolence, anhedonia, reduced motivation, reduced concentration, cravings for methamphetamine and a high rate of relapse to regular use [(7,8)]. Pharmacotherapies aimed at reducing the impact of these symptoms have the potential to reduce relapse risk [(9)].

Despite increasing knowledge regarding the specific neurobiological consequences of methamphetamine use, there is a lack of proven pharmacological approaches to reducing methamphetamine use in dependent individuals [(10, 11)]. Modafinil is an atypical stimulant medication with wakefulness and cognition-enhancing effects [(12)]. It is approved for use in Australia for the

treatment of specific sleep disorders. At doses of 200-400mg daily, modafinil increases synaptic dopamine levels by inhibiting dopamine transporters, with additional action on noradrenaline transporters, and other neurotransmitters including GABA, glutamate and orexin [4, 5].

Interest in modafinil as a pharmacotherapy for methamphetamine dependent individuals relates to its effect on alleviating typical withdrawal symptoms associate with dopamine depletion and reducing cravings for methamphetamine. Its stimulating and cognition-enhancing effects have the potential to reduce methamphetamine relapse triggers, and to potentially enhance engagement with psychosocial treatment modalities to maintain motivation for abstinence. Modafinil is well-tolerated, is regarding to have a low abuse potential and overdose risk, and few adverse effects. Safety has been demonstrated in open-label studies of methamphetamine dependent individuals, including in those concurrently injecting methamphetamine [13, 14, 15].

Three randomised, double-blind, placebo-controlled trials have investigated the effect of modafinil on treatment outcomes for methamphetamine-dependent patients [6,16,17]. At doses of 200-400mg modafinil daily, no significant outcome differences between modafinil and placebo were demonstrated. However, post hoc analysis in one of the trials found a significant difference in methamphetamine abstinence among those with higher medication compliance [17]. Other noted limitations in these studies included small sample sizes, reliance on self-reported outcome measures, and limited engagement in concurrent psychosocial interventions.

The Final Report of the National Ice Taskforce (2015) included a recommendation that the Australian Commonwealth Government should prioritise research into promising pharmacological options for the management of methamphetamine withdrawal and maintenance [18].

An increasing number of Australians are seeking treatment for methamphetamine dependence. Treatment episodes provided by publicly-funded alcohol and other drug services with amphetamine or methamphetamine as the principle drug of concern increased by 123% from 2012-13 to 2016-17 (19). There is evidence of effectiveness for psychological strategies for the treatment of methamphetamine dependence. These strategies include relapse-prevention counselling and Cognitive Behavioural Therapy (CBT) [20]. For many methamphetamine-dependent patients, cognitive deficits and protracted methamphetamine withdrawal symptoms can be a barrier to both accessing and engaging effectively with these forms of treatment [21], predicting both poor treatment retention and clinical outcomes [22].

Drug and Alcohol Services South Australia (DASSA) is a community-based, specialist drug and alcohol treatment service. Among DASSA clinicians, there is some consensus regarding the positive effect of modafinil at alleviating symptoms such as hypersomnolence, poor concentration and low energy in the post-acute phase of methamphetamine withdrawal. These symptoms may otherwise contribute to impaired functioning in daily tasks such as work and caring for children, and be a trigger to methamphetamine relapse. Anecdotally, modafinil may reduce the impetus to use methamphetamine to overcome these deficits, in conjunction with outpatient counselling and psychological interventions. Specifically, modafinil may assist selected patients - those for whom daily, task-orientated function is important - overcome functional impairment in the post-acute withdrawal period, adhere more effectively to psychological treatment, and reduce the risk of relapse to methamphetamine use.

Since October 2016, DASSA has endorsed a clinical guideline for the off-label use of modafinil in selected methamphetamine-dependent patients for up to 3 months to assist with treating protracted withdrawal symptoms and promoting effective engagement with psychological treatment strategies, such as CBT. The protocol was based on open-label, pilot studies conducted at DASSA, and on an evaluation of available literature.

The DASSA outpatient modafinil treatment protocol includes:

- initial assessment and initiation of modafinil either via inpatient acute withdrawal unit or outpatient medical appointment
- modafinil dose range between 100-400mg PO daily; typically as 400mg PO daily for 4 weeks, reducing to 200mg PO daily for 4 weeks, then reducing to 100mg PO daily for a further 4 weeks before cessation
- modafinil dispensed from DASSA outpatient clinics, free of charge to the patient, at 2 weekly intervals
- concurrent non-standardised, individual case-management appointments (including relapse prevention counselling) and medical assessment at intervals of 2-4 weeks.

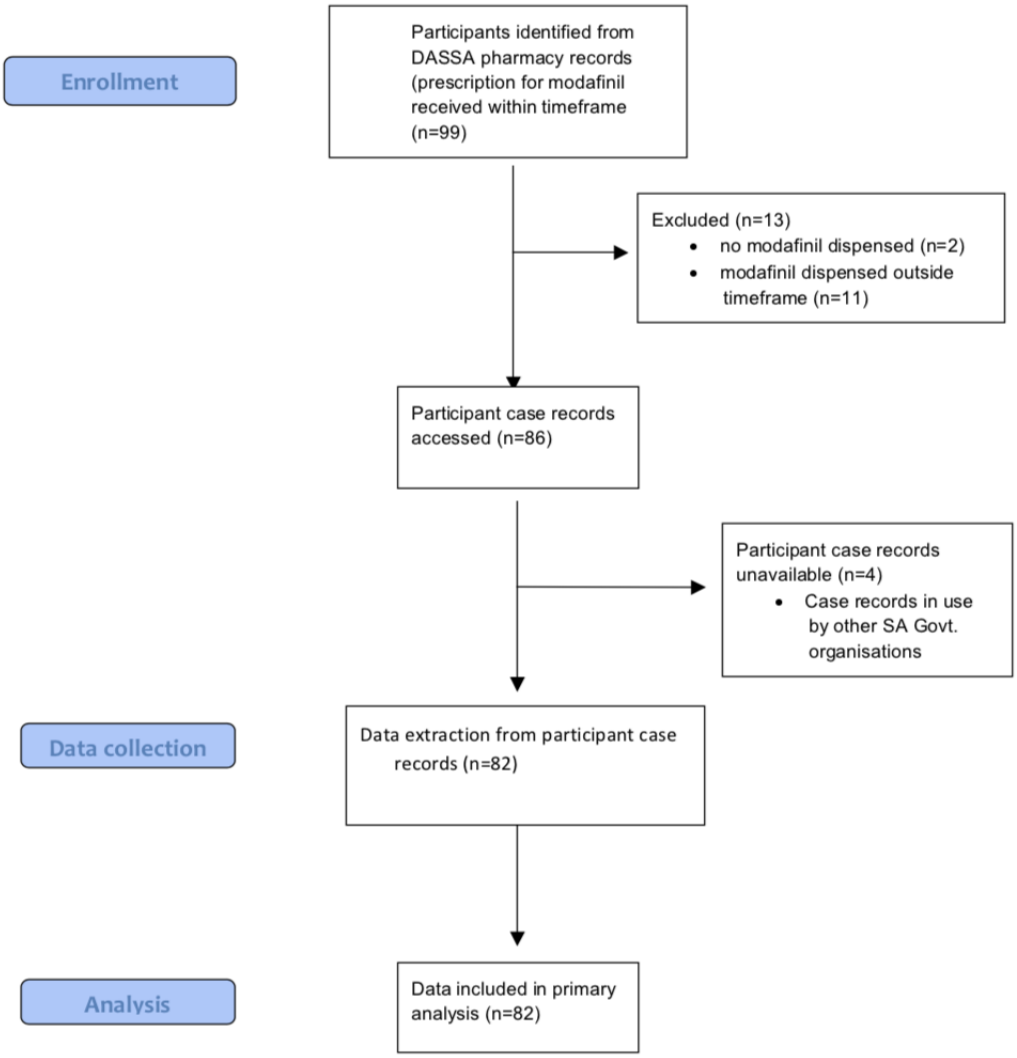
Methodology

The DASSA pharmacy electronic database was accessed to identify outpatients for whom a prescription for modafinil was provided between October 31, 2016 and November 1, 2017. This time period reflected the first twelve months following publication of the DASSA protocol for use of modafinil during outpatient treatment of amphetamine-dependent patients. Ninety-nine patients were identified as meeting these criteria.

Following further interrogation of pharmacy records, 13 patients were excluded from the study sample (modafinil was never dispensed to 2 patients; modafinil was dispensed outside the defined study time period to 11 patients).

Case records of the 86 eligible outpatients were sought from DASSA repositories. Case notes for 4 potential participants were unavailable for data extraction because they were in use by other SA Government organisations, despite best efforts to gain access (see figure 1 below).

Figure 1 Process for identifying eligible outpatient participants from DASSA



A random sample of 10 casenotes was reviewed to assess clinical documentation during outpatient treatment engagement. Based on this review, and on discussion with senior DASSA clinicians who regularly manage patients prescribed modafinil during outpatient treatment for methamphetamine dependence, a set of demographic and substance use characteristic data points were generated which were considered to be clinically relevant to treatment engagement and to perceived positive outcomes with modafinil. A de-identified, coded data extraction database was then created using Microsoft Excel, along with a master coding template detailing instructions and interpretations to ensure consistency of data extraction.

Continuous treatment engagement was defined as documented contact between the patient and a DASSA clinician, indicating treatment adherence (eg attendance at scheduled contact) or intention of adherence (eg, planning/rescheduling contact or telephone contact with a clinician) with an agreed management plan and follow-up schedule. Patients were deemed to have not achieved continuous treatment adherence if appropriate contact had not been documented with 14 days of a scheduled attendance.

All data extraction was performed by the primary researcher (DW).

Ethics approval for this study was obtained from the relevant Human Research Ethics Committee (SAC HREC EC00188; OFR 66.18), along with Site Specific Approval from the DASSA Research Governance Officer.

Data Analysis

Standard descriptive statistics were used to present participant demographics and substance use characteristics.

Univariate assessment of categorical and continuous variables was performed initially, using Pearson chi-square and Fischer exact tests. An alpha level of 0.05 was selected for statistical significance.

Multivariate logistic analysis was subsequently performed on selected variables, which had been identified by discussion among DASSA clinicians during study design as being anecdotally associated with positive outcomes during treatment with modafinil. These included having employment and having children under the age of 16 to care for, among others.

All statistical analyses were performed using IBM SPSS Subscription Software.

Results

Demographics

The sample (n=82) had a median age of 37.4 years at baseline, with a slight male predominance (45, 54.87%). 14 (17.07%) identified with an Aboriginal or Torres Strait Islander cultural background.

66 (80.48%) were unemployed, with 63 (76.82%) receiving some form of government financial benefit. The majority lived in private accommodation, either as a tenant or guest (44, 53.65%) or owner (16, 19.51%). 15 (18.29%) lived in public housing, while the minority were either in temporary hostel accommodation (1, 1.21%) or identified as homeless (6, 7.31%).

26 (31.70%) reported having children under the age of 16 in their care in the same home.

Mental health

There was a high level of reported psychiatric co-morbidity, with 62 (75.60%) reporting a mental health diagnosis (see table 1).

Table 1: Participant demographic characteristics

Age, years (SD)	37.47(7.97)
Male (%)	45 (54.87)
Female (%)	37 (45.12)
ATSI (%)	14 (17.07
Non-ATSI (%)	68 (82.93)
Accommodation (%) Private owner Private tenant/guest Public housing Hostel homeless	 16 (19.51) 44 (53.65) 15 (18.29) 1 (1.21) 6 (7.31)
Kids <16 (%)	26 (31.70)
Employed (%)	16 (19.51)
Benefits (%) None NewStart DSP Parenting payment Other	 19 (23.17) 34 (41.46) 14 (17.07) 13 (15.85) 2 (2.43)
Mental health diagnosis	62 (75.60)

Methamphetamine use

The sample described a mean 11.47 years of methamphetamine use. At baseline, methamphetamine had been used on a mean of 17.13 days out of the preceding 28. Nearly all reported either intravenous injection (45, 54.87%) or smoking (35, 42.68%) as the predominant route of methamphetamine use; only 2 (2.43%) reported usual oral ingestion.

Other substance use

Tobacco was the most commonly used substance aside from methamphetamine, with 59 (71.95%) of the sample reporting use in the preceding 28 days at baseline assessment. This was followed by alcohol (39, 47.56%), cannabis (38, 46.34%) and any benzodiazepine (11, 13.41%). While only 3 (3.65%) participants reported use of a non-prescribed opioid in the preceding 28 days at baseline, 9 (10.97%) were concurrently prescribed methadone or buprenorphine for opioid dependence.

Previous methamphetamine treatment:

57 participants (69.51%) had previously engaged in specialist outpatient counselling for methamphetamine dependence. Just over half (42, 51.21%) had undertaken residential acute withdrawal management (detox), while 9 (10.97% had entered a residential rehabilitation program. Seventeen (20.73%) had previously been prescribed modafinil, in either the acute withdrawal (inpatient) or post-acute withdrawal (outpatient) setting.

Current modafinil treatment

Modafinil treatment during the observation period of this study was initiated during an inpatient acute withdrawal (detox) admission for 38 (46.34%) of the 82 participants, with 44 (53.65%) being commenced following an initial outpatient assessment (see table 2).

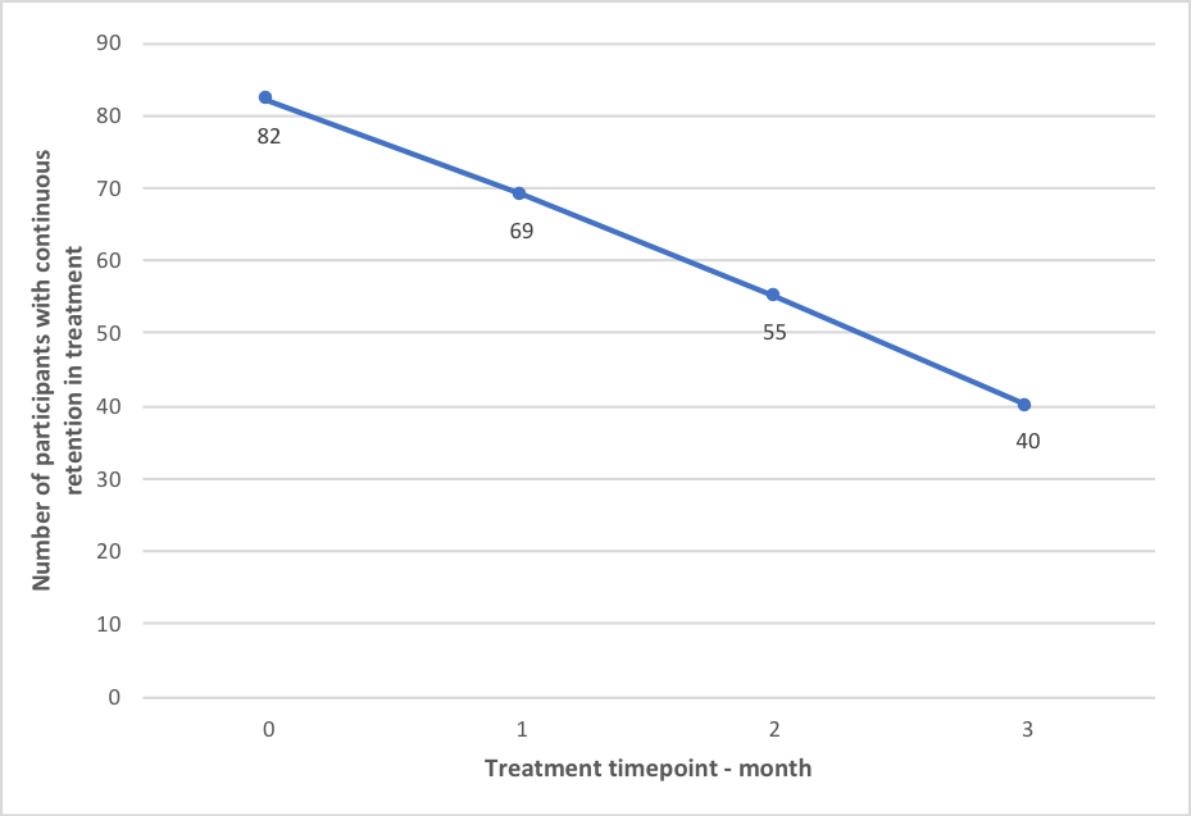
Continuous treatment retention:

Of the 82 participants in the case series, 69 (84.14%), 55 (67.07%) and 40 (48.78%) were continuously engaged in outpatient treatment at the 1, 2, and 3 month time-points, respectively (see table 3, figure 2.)

Table 2: Participant methamphetamine and other substance use characteristics

Years of regular MA use (years, SD)	11.47 (7.84)
MA use in past 28 days (days, SD)	17.13 (9.91)
Primary route of methamphetamine use	
Ingest (%)	2 (2.43)
Smoke (%)	35 (42.68)
IVDU (%)	45 (54.87)
Other substance use in past 28 days	
Alcohol (%)	39 (47.56)
Tobacco (%)	59 (71.95)
Cannabis (%)	38 (46.34)
Opiate (%)	3 (3.65)
Benzodiazepine (%)	11 (13.41)
GHB (%)	2 (2.43)
Cocaine (%)	1 (1.21)
Past MA treatment	
Residential acute withdrawal management (%)	42 (51.21)
Residential rehabilitation (%)	9 (10.97)
Outpatient counselling (%)	57 (69.51)
Previously prescribed modafinil (%)	17 (20.73)

Figure 2: Continuous retention in treatment at 1, 2 and 3 month timepoints



Factors associated with continuous treatment retention to 3 months

Based on both univariate (Pearson chi-square/Fischer exact tests) and multivariate logistic regression analyses, none of the identified patient demographic or substance use characteristic variables were significantly associated with continuous treatment retention to the 3-month time-point (see table 4, table 5)

Table 4: Univariate analysis of participant characteristics and 3 month continuous treatment retention

variable	Continuous treatment retention to 3 months (n=40)	*P* value
Gender (male, %)	22 (55)	0.641
ATSI (%)	7 (17.5)	0.920
Kids >16 (%)	12 (30)	0.746
Employed (%)	9 (22.5)	0.505
Accommodation (%) Private owner Private tenant/guest Public housing Hostel homeless	 7 (17.5) 23 (57.5) 7 (17.5) 1 (2.5) 2 (5)	0.731
Benefit (%) None NewStart DSP Parenting payment other	 9 (22.5) 17 (42.5) 7 17.5) 5 12.5) 2 (5)	0.610
Mental health Dx (%)	29 (72.5)	0.522
MATOD (%)	5 (12.5)	0.666
Previous RR (%)	5 (12.5)	0.666
Previous OPD (%)	29 (72.5)	0.566
Previous modafinil (%)	7 (17.5)	0.481
Years used (SD)	12.57 (7.74)	0.300
Use in past 28 days (SD)	16.33 (10.57)	0.437
Route of MA use (%) Oral Smoked Intravenous	 1 (2.5) 17 (42.5) 22 (55)	0.999
Alcohol use (%)	18 (45)	0.650
Tobacco use (%)	28 (70)	0.701
Cannabis use (%)	20 (50)	0.837
Opioid use (%)	2 (5)	0.528
BZD use (%)	6 (15)	0.648

Table 5: Multivariate analysis of variables and associations with continuous treatment retention at 3 months

Variable	Unadjusted Odds Ratio (95% CI)	*P* value
Male	1.527 (0.478, 4.870)	0.475
Age	1.013 (0.940, 1.092)	0.738
ATSI	0.656 (0.168, 2.566)	0.545
Kids >16	0.519 (0.153, 1.757)	0.292
Employed	0.515 (0.132, 2.003)	0.338
Mental health diagnosis	1.609 (0.472, 5.484)	0.447
MATOD (current)	1.136 (0.198, 6.526)	0.886
Previous inpatient withdrawal	1.557 (0.451, 5.372)	0.483
Previous residential rehabilitation	0.601 (0.120, 3.001)	0.535
Previous outpatient counselling	0.718 (0.208, 2.474)	0.599
Previously prescribed modafinil	1.488 (0.379, 5.841)	0.569
Years of methamphetamine use	1.037 (0.954, 1.127)	0.391
MA use in past 28 days	0.999 (0.947, 1.054)	0.977

Similarly, odds ratios derived from the logistic regression model did not demonstrate an association between the selected variables and the primary outcome of continuous treatment retention at 3 months. (see table 5).

The logistic regression model achieved an overall accuracy (*percentage correct)* of 66.2%.

Discussion

This single-organisation, retrospective case series describes a sample of patients prescribed modafinil during outpatient treatment of methamphetamine dependence. While there was no evidence of association between the analysed variables and the primary outcome of continuous treatment retention at 3 months. The observational and outcome data is valuable, given the lack of evidence-based pharmacological treatments for methamphetamine dependence. Modafinil is identified in the literature as a novel pharmacology of interest, which has been shown to be safe and well-tolerated. DASSA seems to be unique among Australian drug and alcohol treatment services in offering modafinil as an off-label adjunct to psychosocial interventions for methamphetamine dependence in the outpatient setting.

Almost half of the participants from this case series achieved continuous treatment retention to 3 months. This is a positive observation in the context of limited Australian data relating to treatment retention for methamphetamine dependent individuals. The demographic and drug use characteristics of the study cohort presented are generally consistent with Australian data related to methamphetamine dependent patients seeking treatment.

The Methamphetamine Treatment Evaluation Study (MATES) included 360 participants from multiple community-based treatment centres in Sydney and Brisbane (23). MATES had a number of similarities regarding demographic and substance use characteristic when compared to the presented case series: the MATES cohort had a median age of 35, with 84% unemployment. Baseline methamphetamine use in the MATES cohort was 16 out of the past 28 days, but with a higher proportion of intravenous use (73%). MATES demonstrated similarly high rates of psychiatric comorbidity and concurrent substance use, particularly tobacco, cannabis and alcohol. The median duration of counselling episodes in MATES was 71 days.

The Australian Institute of Health and Welfare (AIHW) recently published data for 2016-17 from 836 publicly-funded drug and alcohol treatment services, comprising more than 200,000 treatment episodes for over 127,000 clients. 26% of all completed treatment episodes related to amphetamine/methamphetamine use, second only behind alcohol (32%). The median duration of all counselling episodes (any substance) was 54 days. Episodes related to amphetamine/methamphetamine had a median duration of 29 days, which included interventions ranging from assessment only to case-management, withdrawal management, counselling and residential rehabilitation (AIHW 2018)

Continuous treatment retention is an outcome of significance for methamphetamine-dependence. There is strong evidence demonstrating that methamphetamine use, along with physical, emotional and social outcomes are improved with continuity of treatment [23, 24].

While the presented case series demonstrated positive outcomes in terms of treatment retention for outpatient methamphetamine dependent clients, there are a number of limitations that frame the observations presented.

The lack of a control group meant there was no opportunity to compare characteristics and continuous treatment retention to those prescribed modafinil. For participants included in this study, there is a selection bias attributable to individual clinician assessment of suitability for modafinil. A follow-up study should include a comparison group of methamphetamine-dependent participants offered the same structure of outpatient psychosocial support, without receiving modafinil. There should also be clearly defined parameters for determining patient eligibility for modafinil.

While evidence demonstrates that modafinil is well-tolerated in methamphetamine-using populations and has a low risk of adverse effects, due to variability in documentation at clinical assessment, this case series was not able to consistently identify adverse medication effects. This may have negatively impacted continuous treatment retention for individual participants, and would be important to explore in future studies of this population.

Previous studies of modafinil have commented on the potential impact on outcomes of poor medication adherence. Medication adherence was not able to be consistently identified in this case series, but should be documented and, ideally, optimised in subsequent studies.

For participants in this case series, individual case management was offered. This is consistent with the evidence base for psychosocial interventions in treating methamphetamine dependence. However, there was no formal or consistent approach to type of case-management or relapse-prevention counselling support offered. It is possible that this variability may have impacted the continuous treatment engagement of individual participants.

Among this study population, there was not a standardised approach to follow-up of participants who disengaged with treatment. Individuals may have stopped accessing treatment for a range of reasons, including perceived treatment success, perceived treatment failure/inadequacy, or difficulty accessing treatment (eg, imprisonment, poor health or changed social circumstances). Identifying reasons for disengagement would be important to better understand factors impacting continuous treatment retention.

Data extraction for this retrospective study was limited by contemporaneous clinical documentation. Without a standardised/template for assessment during treatment with modafinil, the consistency of information obtained was noted to be variable.

Consultation among DASSA clinicians and standardisation of assessments for future patients is likely to improve inter-participant variability and increase protocol adherence. A formal clinical audit of the DASSA modafinil protocol would enhance the opportunity to assess clinical outcomes and effectiveness of the intervention.

A subsequent, prospective study should include other outcome measures, such as urine drug screening and consistent and standardised self-reporting of methamphetamine use. Self-reported or standardised measures of medication effect such as craving, function, sleepiness, alertness or other cognitive assessment measures may also provide better insight into the effect of modafinil in this population.

Univariate analyses of the data presented did not demonstrate a statistically significant association between individual participant characteristics and the outcome of continuous treatment retention at 3 months. Multivariate logistic regression models should ideally include independent variables with a high likelihood of association with the outcome of interest – the dependent variable - which in this case was continuous treatment retention at 3 months. In this instance, considering the results of the univariate analyses, variables were selected for inclusion in the logistic regression model based on DASSA clinician consensus opinion of the likelihood of association with the selected outcome. The unadjusted odds ratios generated by the multivariate logistic regression model did not demonstrate an association between the analysed variables and continuous treatment retention at 3 months. The large associated confidence intervals are likely to reflect the effect of small sample sizes and unidentified variables.

As an observational case series, this study did not intend to analyse the effectiveness of modafinil as a treatment for methamphetamine dependence. Case series are descriptive, and do not set out to test hypotheses related to treatment efficacy. Large numbers and effect sizes are needed to make positive observations regarding outcomes in case series. However, case series reports have recognised utility in improving case definition, providing clues and trends regarding outcomes, and in generating hypotheses and informing further follow-up studies [25].

Conclusion

Methamphetamine dependence is a significant public health issue facing Australian communities. Changes in patterns of use among people who use methamphetamine, along with increased potency of the substance are contributing to a significant burden of physical, psychiatric and social harms.

There are no pharmacological agents with robust efficacy or effectiveness in managing methamphetamine dependence. Standardised behavioural interventions have a positive evidence base, but enduring effects are strongly associated with continuous treatment engagement. Methamphetamine dependent individuals may experience a number of barriers to effective engagement with behavioural interventions, and relapse rates remain high. Modafinil profiles as a safe pharmacological agent when used in methamphetamine dependent populations, and may represent a strategy to enhance engagement with behavioural interventions. A small number of randomised controlled and open label clinical trials of modafinil for treatment methamphetamine dependence in the outpatient setting have not demonstrated significant effect, but limitations relating to sample size and medication compliance have been noted. There is consensus regarding the need to continue to identify evidence-based pharmacological approaches to treating methamphetamine dependence.

This study describes demographic and substance-use characteristics of this consistent with Australian data relating to populations seeking treatment for methamphetamine dependence. While no participant variables were identified as being associated with longer treatment engagement, the study positively observed continuous retention in treatment of almost 50% of the sample over a three-month period.

Further investigation of this patient group, including a prospective research design to overcome limitations associated with the presented case series, would facilitate evaluation of the DASSA modafinil protocol and enhance understanding of modafinil as a potential pharmacotherapy for methamphetamine dependence.

Bibliography

1. Degenhardt L et al. Crystaline methamphetamine use and methamphetamine-related harms in Australia. Drug and Alcohol Review 2017;36(2):160-170.
2. Australian Institute of Health and Welfare. (2017). National Drug Strategy Household Survey 2016: detailed findings. Retrieved from https://www.aihw.gov.au/reports/illicit-useof-drugs/2016-ndshs-detailed/contents/table-of-contents
3. National Drug Research Institute. Responding to methamphetamine use and harms in Australia: A submission to Parliamentary Joint Committee on law enforcement's inquiry into crystal methamphetamine (ICE). Curtin University. June 2015.
4. Morley, K et al. Pharmacotherapeutic agents in the treatment of methamphetamine dependence. Expert Opinion on Investigational drugs (2017); 26(5):563-578.
5. Ballester J, Valentine G and Sofuoglu M. Pharmacological treatments for methamphetamine addiction: current status and future directions. Expert Review of Clinical Pharmacology 2017;10(3):305-314.
6. Shearer J. et al. A double-blind, placebo-controlled trial of modafinil (200mg/day) for methamphetamine dependence. Research Report. 2009. Society for the Study of Addiction. doi:10.1111/j.1360-0443.2008.02437.x
7. Hart CL et al. Is cognitive functioning impaired in methamphetamine users? A critical review. Neuropsychopharmacology 2012;38:259-274.
8. Brensilver M, Heinzerling K, Shoptaw S. Pharmacotherapy of amphetamine-type stimulant dependence: An update. Drug and alcohol review 2013;32:449-460.
9. Mereu M et al. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorder. Psychopharmacology 2013;229(3):415-434
10. Courtney K. and Ray L. Methamphetamine: an Update on Epidemiology, Pharmacology, Clinical Phenomenology, and Treatment Literature. Drug and Alcohol Dependence. 2014 October; 0:11-21.
11. Härtel-Petri, R et al. Evidence-Based Guidelines for the Pharmacologic Managament of Methamphetamine Dependence, Relapse Prevention, Chronic Methamphetamine-Related, and Comorbid Psychiatric Disorders in Post-Acute Settings. Pharmacopsychiatry 2017; 50: 96-104.
12. Stoops W., Lile J., Fillmore M., Glaser P., Rush C. Reinforcing effects of modafinil: influence of dose and behavioural demands following drug administration. Psychopharmacology 2005; 182: 186–93.
13. McElhiney MC et al. Provigil (modafinil) plus cognitive behavioural therapy for methamphetamine use in HIV+ gay men: a pilot study. American Journal of Drug and Alcohol Abuse 2009;35:34-37.
14. McGaugh J, Mancino MJ, Feldman Z, et al. Open-label pilot study of modafinil for methamphetamine dependence. *J Clin Psychopharmacol*. 2009;29(5):488-91.
15. De La Garza R et al. Evaluation of modafinil effects on cardiovascular, subjective and reinforcing effects of methamphetamine in methamphetamine-dependent volunteers. Drug and Alcohol Dependence 2010;106(2-3):173-180.
16. Heinzerling K. et al. Randomised, double-blind, placeba-controlled trial of modafinil for the treatment of methamphetamine dependence. Drug and Alcohol Dependence. 2010 June 1; 109(1-3):20-29.

17. Anderson A. et al. Modafinil for the treatment of Methamphetamine Dependence. Drug and Alcohol Dependence. 2012 January 1; 120(1-3): 135-141.
18. Department of the Prime Minister and Cabinet. (2015). Final Report of the National Ice Taskforce 2015. Retrieved from https://www.pmc.gov.au/sites/default/files/publications/national_ice_taskforce_final_report.pdf
19. Australian Institute of Health and Welfare 2018. Alcohol and other drug treatment services in Australia: 2016–17. Drug treatment series no. 31. Cat. no. HSE 207. Canberra: AIHW.
20. Lee N and Rawson R. A systematic review of cognitive and/or behavioural therapies for methamphetamine dependence. Drug and Alcohol Review 2015;27(3):309-317. Ghahremani DG et al. Effects of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. Neuropsychopharmacology 2011;36(5):950-959.
21. Sofuoglu M et al. Cognitive enhancement as a treatment for drug addictions. Neuropharmacology 2013;64:245-250.
22. McKetin R et al. Evaluating the impact of community-based treatment options on methamphetamine use: findings from the Methamphetamine Treatment Evaluation Study (MATES). Addiction 2012;107(11):1998-2008.
23. Manning V et al. Substance use outcomes following treatment: Findings from the Australian Patient Pathways Study. The Australian and New Zealand Journal of Psychiatry 2017;51(2):177-189.
24. Carey T, Boden S. A Critical Guide to Case Series Reports. Spine 2003;28(15):1631-1634.

For more information contact:

Office of the Clinical Director
Drug and Alcohol Services South Australia
75 Magill Road, Stepney SA 5069
Tel: (08) 7425 5000