Modafinil and mirtazapine for management of amphetamine withdrawal

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Background

- Amphetamine dependence is an important public health issue in Australia
- There has been significant increase in the use of the crystal form of methamphetamine ('ice') over the last 10 years[1].
- Amphetamine withdrawal commonly manifests with sleep-wake cycle disturbance[2].
- Current Drug and Alcohol Service South Australia (DASSA) protocols recommend the off-label use of modafinil or mirtazapine for patients meeting certain criteria e.g. excessive daytime sleeping
- Literature provides some support for the use of modafinil and mirtazapine in the treatment of amphetamine dependence in the outpatient setting but is limited in the inpatient setting[3]
- A 2008 DASSA study indicated some efficacy of these medications for in-patient withdrawal[4]
- This study sought to investigate the effect of these drugs on a range of treatment outcomes in the setting of inpatient withdrawal

Modafinil: a novel, non-amphetamine stimulant indicated in narcolepsy and sleep disorders

Mirtazapine: a tetracyclic antidepressant with sedative and anxiolytic effects indicated for Major Depression

Aim: To assess the effectiveness of modafinil and mirtazapine, compared with treatment as usual, in the management of acute amphetamine withdrawal.

Research Questions:

- Does the use of modafinil in withdrawal aid in treatment completion compared with treatment as usual?
- Does the use of mirtazapine in withdrawal aid in treatment completion compared with treatment as usual?
- What impact do modafinil and mirtazapine have on sleep quality and sleep-wake cycle disturbance compared with treatment as usual?
- What impact do modafinil and mirtazapine have on symptom severity compared with treatment as usual?

Method:

- File numbers were extracted from the DASSA database based on the following criteria: **Inpatient** admissions in **2016** with **amphetamine** or **methamphetamine** as the **primary drug of concern**.
- Client records were able to be accessed at DASSA Central Repository and included episodes from the Northern, Southern, Central and Regional networks.
- Data collected for each episode included:

  Demographic data, mental health status, previous admissions, injecting status, current medications, medications received during withdrawal, treatment outcomes, day of administration of modafinil or mirtazapine and discharge status (complete or incomplete treatment)
- Scoring for the St Mary's Hospital Sleep Questionnaire, objective and subjective Amphetamine Cessation Symptomatic Assessment Score (ACSA)[4] and score of sleep-wake cycle disturbance extracted from clinical assessment of sleep quality.

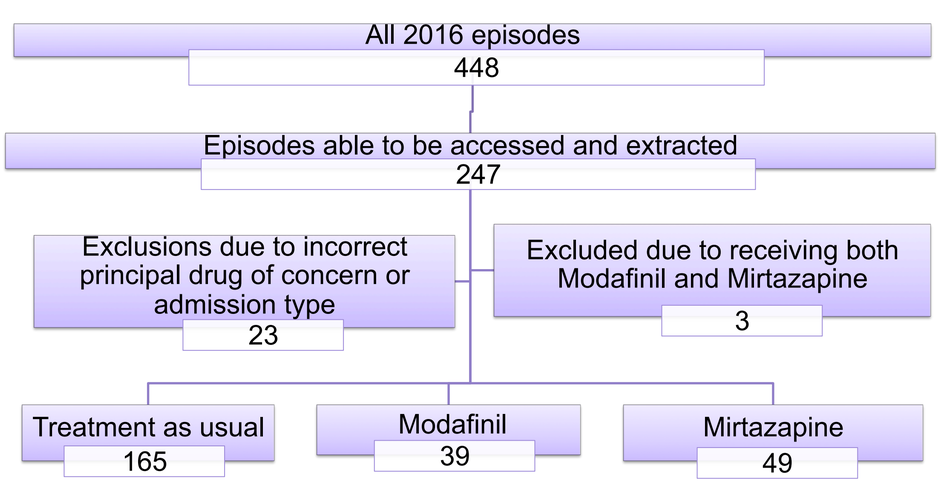

Figure 1: Refinement of cohort

Statistical Analysis:

- Logistic regression used to analyse treatment completion due to binary outcomes and adjustment for variables
- Scatter plots used to assess trajectory patterns of symptom severity and sleep-wake cycle disturbance

Results

Cohort	Gender *n*(%)		Indigenous *n*(%)	Injecting *n*(%)	Polydrug Use *n*(%)	Previous Inpatient Withdrawal *n*(%)	Treatment Outcome *n*(%)		Mental Health Diagnosis *n*(%)
	Male	Female					Completed	Not Completed	
Treatment as Usual	101 (61.2)	64 (38.8)	38 (23.0)	111 (67.3)	131 (79.4)	76 (46.1)	99 (55.2)	74 (44.8)	137 (83.0)
Modafinil	22 (56.4)	17 (43.6)	1 (2.6)	25 (64.1)	30 (76.9)	25 (64.1)	31 (79.5)	7 (17.9)	31 (79.5)
Mirtazapine	34 (69.4)	15 (30.6)	7 (14.3)	36 (73.5)	43 (87.8)	25 (51.0)	19 (38.8)	29 (59.2)	44 (89.8)
Total	158 (61.5)	98 (38.1)	46 (17.9)	174 (67.8)	206 (80.2)	128 (50.6)	143 (56.5)	111 (43.9)	214 (84.6)

Figure 2: Cohort demographics

Logistic regressions of treatment completion adjusted for confounding factors

Group	Odds Ratio	Std Error	*P* Value	95% Confidence Interval
Treatment Completion				
Number of obs = 252				
Modafinil	3.60	1.61	0.004	1.50, 8.65
Mirtazapine	0.52	0.17	0.046	0.27, 0.99
Treatment completion adjusted for mental health diagnosis				
Number of obs = 251				
Modafinil	3.55	1.59	0.005	1.48, 8.54
Mirtazapine	0.51	0.17	0.042	0.26, 0.98
Treatment Completion adjusted for clinically significant anxiety				
Number of obs = 229				
Modafinil	3.06	1.40	0.014	1.25, 7.49
Mirtazapine	0.49	0.17	0.039	0.24, 0.96

Sleep Quality

- Scatter plots of SMHSQ scoring by day of treatment showed no clear pattern between groups
- Trajectory plots linking individual observations demonstrated no consistent pattern in any group
- No difference evident between modafinil and mirtazapine groups when adjusted for day of treatment administration

Sleep-Wake Cycle Disturbance

- Trajectories of sleep wake cycle disturbance score showed no difference in pattern between groups
- Tabulation of scoring demonstrated minimal reports of 'severe' sleep wake cycle disturbance in any group
- Logistic regression of severe sleep-wake cycle disturbance compared with treatment as usual:
  - Modafinil: 1.78 (95% CI 0.52, 6.13; *P*=0.36)
  - Mirtazapine: 1.00 (95% CI 0.21, 4.867; *P*=0.99)

Symptom Severity

- Scatter plots of total daily withdrawal scoring show no clear difference between groups
- Downward trajectory after Day 4; around 50% attrition after day 4
- More severe withdrawal on admission unlikely to play a role in discharge prior to day 4 treatment

Discussion:

- Modafinil was associated with a higher likelihood of completing treatment (i.e. being 'Discharged as planned") compared with treatment as usual
- Mirtazapine was associated with a decreased likelihood of completing treatment compared with treatment as usual
- Adjustment of regressions for mental health diagnosis and clinically significant anxiety yielded minimal difference – reasoning behind mirtazapine potentially having a detrimental effect requires further investigation
- Minimal difference identified between groups in terms of symptom severity and sleep-wake cycle disturbance however this is potentially due to identified limitations in subjective/objective scoring tools used.
- Consultation with clinicians at DASSA following study identified potential unidentified selection bias towards certain patient types in modafinil group.
- Dosing of mirtazapine appears to be commonly too high to produce sedative effect

Future Directions:

- Positive outcomes for modafinil patients may indicate promise for RCT to substantiate its efficacy
- It is important to determine if there is a subgroup of patients who respond well to modafinil and benefit from modafinil post withdrawal e.g. patients initiating amphetamines for functional purpose (e.g. more efficiency/ energy at work).
- Administration time of Mirtazapine should be reviewed with consideration given to an alternative regime (e.g. administered in the morning) and review of rationale for dosing.
- Further consideration of limitations of study should be taken into account, including effectiveness of measurement tools such as St Mary's Hospital Sleep Questionnaire and ACSA

References:

[1]Stafford J &Breen C (2015) *Australian Drug Trends Series,* National Drug and Alcohol Research Centre.

[2]McGregor C et al (2005) *Addiction*. **100,** 1320-9.

[3]Brensilver M et al (2013). *Drug Alcohol Rev*. **32,** 449-460.

[4]McGregor C et al (2008). *J. Subst Abuse Treat*. **35,** 334-342.

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