4. CHAPTER 4: DEVELOPMENT AND PSYCHOMETRIC TESTING OF THE AMPHETAMINE CESSATION SYMPTOM ASSESSMENT SCALE

4.1. Introduction

Signs and symptoms arising in the initial phase of abstinence are of substantial interest to clinicians involved in the management of patients with substance dependence. The withdrawal syndrome associated with drugs of dependence such as alcohol, opioids, nicotine, benzodiazepines, cocaine and marijuana have been characterised (Handelsman *et al.*, 1987; Tyrer *et al.*, 1990; Weddington *et al.*, 1990; Satel *et al.*, 1991; Sullivan *et al.*, 1991; White *et al.*, 1994; Jorenby *et al.*, 1996; Budney *et al.*, 1999; Kenny & Markou, 2001). However, the measurement of the amphetamine withdrawal syndrome has lagged behind that for other drugs of dependence as noted by two recent major reviews of the field (Srisurapanont *et al.*, 2003; Baker *et al.*, 2004).

The paucity of empirical data regarding amphetamine withdrawal and its treatment is surprising in view of the long history of amphetamine 'epidemics' occurring in a number of countries (Hall & Hando, 1993), the widespread and increasing use of amphetamines internationally (United Nations Office on Drugs and Crime, 2003) and the documented risks associated with amphetamine use, both to the amphetamine user and to the wider community (Hall *et al.*, 1996; Vincent *et al.*, 1998; Byqvist, 1999; Wright & Klee, 2001; Brecht & Greenwell, 2002).

An important next step in the investigation into the nature and treatment of amphetamine withdrawal was to use the data already collected to develop and test a new instrument for the measurement of withdrawal symptoms in amphetamine dependent individuals. This chapter will describe the process of assessing the two questionnaires used in both the Australian and Thai withdrawal studies (described in **Chapters 2** and **3**) to identify items suitable for incorporation into a single comprehensive amphetamine withdrawal instrument.

The availability of a comprehensive instrument that was also valid and reliable carries significant implications for diagnosis and treatment evaluation in respect to amphetamine dependence and withdrawal. This instrument would be useful in three main areas, specifically:

i) as a means of monitoring changes in symptoms among amphetamine dependent clients in treatment,

ii) testing and outcome evaluation of interventions into amphetamine dependence and/or withdrawal and

iii) guiding the development of new treatment protocols in amphetamine withdrawal and dependence.

4.1.1. Background amphetamine withdrawal studies

Studies of amphetamine withdrawal in Australia and Thailand (see **Chapters 2 and 3**) are summarised briefly below. Both withdrawal studies aimed to identify the nature, time course and severity of symptoms experienced by dependent amphetamine users on cessation of regular use. Twenty amphetamine-dependent inpatients in Adelaide, Australia (see **Chapter 2**) were involved in the first study. The second study (see **Chapter 3**) involved 21 amphetamine-dependent inpatients in Chiang Mai, Thailand (McGregor, Srisurapanont, Jittiwutikarn, Laobhripatr, Wonttan & White, 2003, 2003; McGregor *et al.*, 2005). Together, these studies provided data from 41 subjects (20 in Australia and 21 in Thailand).

The research designs for both studies were similar. Subjects were drawn from consecutive admissions to two inpatient substance use facilities (Warinilla Clinic in South Australia and the Northern Drug Dependence Treatment Centre, Chiang Mai, Thailand) for inpatient amphetamine dependence treatment. Subjects included in the samples were aged between 18 and 45 years, fulfilled the DSM-IV criteria for amphetamine dependence (DSM-IV-TR, 2000) and could provide a urine sample positive for sympathomimetic amines, a marker for recent amphetamine use. Excluded from the sample were those who exhibited concurrent acute medical or psychiatric illness requiring psychotropic medication or acute care hospitalisation; or who fulfilled the DSM-IV diagnostic criteria for other substance dependence, except nicotine. Subjects gave written informed consent prior to data collection. There was no compensation for study participation. The Human Research Ethics Committee of the University of Adelaide and the Ministry of Public Health in Thailand provided ethics approval.

The first of two instruments used to measure amphetamine withdrawal symptoms was the Amphetamine Withdrawal Questionnaire (AWQ) (Srisurapanont *et al.*, 1999), a 10 item, self-completed instrument based on DSM-IV withdrawal criteria, that measures amphetamine craving, dysphoria, anhedonia, increased appetite, fatigue, agitation, anxiety, increased sleep, vivid, unpleasant dreams and motor retardation over the previous 24 hours. The possible range of aggregate scores is 0 – 40 with higher numbers indicating greater severity.

The second scale, the Cocaine Selective Severity Assessment (CSSA) (Kampman *et al.*, 1998) was modified for use in both preliminary studies. The only modification made to the 18-item CSSA was the replacement of 'cocaine' with 'amphetamine'. Thus the CSSA became the ASSA. Domains measured by this scale were: increased or decreased appetite, increased or decreased sleep, intensity and frequency of craving for amphetamine, craving for carbohydrate, bradycardia, difficulty concentrating, irritability, anxiety, depression, paranoid and suicidal ideation, tension, anhedonia, inactivity and fatigue over the previous 24 hours. The possible range of aggregate scores is 0 – 112, higher scores indicated greater severity.

The withdrawal studies conducted in Australia and Thailand provided important information on the nature, time course and severity of the amphetamine withdrawal syndrome. The time course and severity of amphetamine withdrawal having been characterised, it was now possible to identify the main symptoms that occurred on cessation of dependent amphetamine use. However, while the Amphetamine Withdrawal Questionnaire (Srisurapanont *et al.*, 1999) provided valuable information on a range of withdrawal symptoms, the modified version of the Cocaine Selective Severity Assessment (Kampman *et al.*, 1998) was also sensitive to changes over the acute and sub acute withdrawal phases. Use of the modified version of the CSSA also provided additional information over and above that provided by the AWQ on a range of symptoms, notably poor concentration, tension and inactivity.

4.1.2. Aim

The aim of the work described in this chapter was to develop a valid and reliable instrument for the measurement of symptoms emerging in amphetamine dependent clients on cessation of regular use.

The following section describes the process of item analysis, factor analysis and item selection using the combined withdrawal symptom data from the studies reported in **Chapters 2** and **3**. The procedure for item analysis as described by Kline (Kline, 1998) was used as a guide (see below).

i) Administer a pool of items to a representative sample of subjects for whom the test is intended

ii) Compute item-total correlations

iii) Select those items which correlate with the total score at greater than 0.30

iv) Administer the new pool of items to a new sample

v) Compute reliability and execute validation studies of the new test

Guideline (i) was addressed by the work described in **Chapters 2** and **3** above. Guidelines (ii) and (iii) will be addressed by the work in the First Section (see **Section 4.2 below**) of this chapter. Guidelines (iv) and (v) were addressed by the work described in the Second Section (see **Section 4.3 below**) of this chapter. Additionally, principal components analysis was used to identify the factor structure of the AWQ and the ASSA and to assist in item selection (Nunnally & Bernstein, 1994).

4.2. Section 1: Development of the new amphetamine withdrawal instrument

4.2.1. Scale data set

To conduct the initial reliability analysis, data from both Australian and Thai withdrawal studies were combined to provide a sample size of 41 subjects. Only

data from the first week was used as that period was identified as being the acute phase of withdrawal. All data collected during the Australian withdrawal study (days 0 – 7 of abstinence) and the first eight days of data from the Thai study (days 0 – 7 of abstinence) were included in the data set. Therefore, the total sample comprised 41 subjects who completed both the AWQ and the ASSA daily for between one and eight days. The combination of the two data sets provided a total of 214 administrations of each withdrawal scale for analysis.

4.2.2. Data analysis plan

Firstly, item analysis (Cronbach's alpha) was used to eliminate redundant or poorly performing items. Secondly, items were submitted to a principal component analysis (PCA). Finally, an oblique rotation was performed to identify the factor structure of the scales.

4.2.3. Reliability analysis, ASSA

Internal consistency reliability to test unidimensionality was assessed by Cronbach's alpha and corrected item-total correlations**. Table 4.1** details the reliability analysis of the 18 ASSA items. At 0.74, Cronbach's alpha for this instrument showed satisfactory internal consistency (Nunnally & Bernstein, 1994) indicating that the scale items were reliably measuring the same trait. However, scale dimensionality was further assessed by PCA (see **Section 4.2.5 below**).

Thirteen of the 18 items showed corrected item total correlations that met the criterion for retention (i.e., > 0.30). Five items; hypophagia (decreased appetite), hyperphagia (increased appetite), carbohydrate craving, bradycardia and hyposomnia did not meet the criterion for retention and were flagged for exclusion. Inter item correlations were satisfactory with no redundant items identified. At r = 0.81, anxiety showed the highest inter item correlation.

Table 4.1 Reliability analysis, ASSA

Item	Corrected item-total correlation	Alpha if item deleted
Anxiety	0.81	0.71
Tension	0.79	0.72
Irritability	0.78	0.72
Anhedonia	0.76	0.71
Depression	0.71	0.72
Fatigue	0.70	0.72
Craving intensity	0.69	0.72
Craving frequency	0.69	0.72
Concentration	0.54	0.73
Inactivity	0.52	0.72
Suicidal ideation	0.52	0.73
Paranoid ideation	0.48	0.73
Hypersomnia	0.34	0.73
*Carbohydrate craving	0.29	0.73
*Hypophagia	0.27	0.74
*Bradycardia	0.26	0.75
*Hyposomnia	0.21	0.74
*Hyperphagia	0.17	0.74

*Item total correlation of < 0.30

4.2.4. Reliability analysis, AWQ

As for the ASSA, the internal consistency reliability to test unidimensionality was assessed for the 10 AWQ items by Cronbach's alpha and corrected item-total correlations (see **Table 4.2**). The resulting alpha value of 0.77 was above the acceptable threshold (0.70) suggested by Nunnally & Bernstein (1994) indicating that the AWQ possessed satisfactory internal consistency and that the scale items

were reliably measuring the same trait. Dimensionality of the scale was further assessed by PCA (see **Section 4.2.5 below**). Although this level of internal consistency is satisfactory for a test of this nature, one way of increasing reliability (as measured by Cronbach's alpha) is to add more items to the instrument. Application of the Spearman-Brown Formula indicated that the addition of six further items to the 10 item AWQ would raise the alpha level to 0.84, thereby increasing the reliability from 'satisfactory' to 'good' (Kaplan & Saccuzzo, 1989).

Table 4.2 Reliability analysis for the AWQ

Item	Corrected item-total correlation	Alpha if item deleted
Anxiety	0.84	0.73
Agitation	0.84	0.73
Dysphoria	0.80	0.74
Anhedonia	0.80	0.74
Motor retardation	0.74	0.74
Fatigue	0.70	0.74
Craving	0.69	0.74
Vivid dreams	0.62	0.75
Increased sleep	0.49	0.76
*Increased appetite	0.21	0.77

*Item total correlation < 0.30

Nine of the ten AWQ items met the generally accepted criterion for retention in a scale i.e., corrected item-total correlations of >0.30 (Nunnally & Bernstein, 1994; Kline, 1998). Only one item (increased appetite) did not meet this criterion and was flagged for exclusion from the new instrument. Inter item correlations were satisfactory with no redundant items identified. At r = 0.84, anxiety and agitation showed the highest inter item correlation.

Both the ASSA and the AWQ were then subjected to PCA to investigate further the utility of individual items in the proposed new instrument.

4.2.5. Principal Components Analysis, ASSA

The 18 items of the ASSA were subjected to PCA using SPSS. Prior to performing the PCA, the suitability of data for factor analysis was assessed. Data were normally distributed with a number of coefficients of 0.30 and over. No outliers were identified. The Kaiser-Meyer-Olkin value was 0.87, exceeding the recommended value of 0.60 (Kaiser, 1974) and the Bartlett's Test of Sphericity (Bartlett, 1954) reached statistical significance, supporting the factorability of the correlation matrix.

4.2.6. Rotation, ASSA

Exploratory rotation of the 18 ASSA items was carried out to identify relationships between factor scores. Five factors or components[3] were revealed and an examination of the factor score correlation matrix revealed a correlation of $r = 0.32$ between components two and five. The relatively strong relationships between components were not unexpected as high factor score correlations are commonly found in assessments of psychiatric conditions (Nunnally & Bernstein, 1994). As the correlations between factor scores exceeded the cut-off point of 0.30 for the use of varimax rotation (the mostly commonly used technique), an oblique rotation that allows for correlated factor scores was selected as the most appropriate technique for the present data set (Tabachnick & Fidell, 2001).

In the next stage, an oblique rotation of items was applied to the unrotated factor matrix to yield a maximally interpretable solution. A cut-off score of 0.30 was used for item loading. Loadings of < 0.30 account for less than 9% of the variance and contribute little to the factor (Tabachnick & Fidell, 2001; Kline, 2002). The rotated solution (see **Table 4.3**) showed a number of strong loadings and all items were assigned to a factor. The presence of five components with eigenvalues exceeding 1 that explained a total of 68.3% of the variance was revealed. The five component solution explained 37% (eigenvalue = 6.7), 10.3% (eigenvalue = 1.90),

[3] The terms 'factor' and 'component' will be used interchangeably.

9.1% (eigenvalue = 1.70), 6% (eigenvalue = 1.08) and 5.7% (eigenvalue = 1.03) of the variance respectively.

Rotation converged in 24 iterations. While there is some divergence of opinion as to whether the structure or the pattern matrix should be reported in oblique rotation (Kline, 2002), most authors report the pattern matrix as it offers a more easily interpretable result (Tabachnick & Fidell, 2001). In the present study the pattern matrix is reported as the output lends itself to a clearer interpretation in comparison to the structure matrix.

Table 4.3 Pattern Matrix, ASSA

	Component				
	1	**2**	**3**	**4**	**5**
Paranoid ideation	0.79				
Suicidal ideation	0.77				
Depression	0.70				
Irritability	0.62				
Tension	0.57				-0.35
Anxiety	0.48	0.39			
Inactivity		0.89			
Fatigue		0.69			
Anhedonia		0.69			
Hypersomnia		0.60	0.53		
Poor concentration	0.30	0.49			
Hyposomnia	0.33		-0.71		
Hyperphagia			0.64		
Hypophagia		0.35	-0.61		
Carbohydrate craving				-0.81	
Bradycardia				0.72	
Craving intensity					-0.81
Craving frequency					-0.80

Of the 18 ASSA items, six: tension, anxiety, hypersomnia, poor concentration, hyposomnia and hypophagia loaded onto two components with a loading of >0.30. The remaining 12 items met simple-structure criteria (at least 0.30 on a home factor and < 0.30 on all other factors) (Thurstone, 1947; Kline, 1998).

The loading of items measuring hypophagia (decreased appetite), hyperphagia (increased appetite), carbohydrate craving, bradycardia and hyposomnia on the weaker components together with an item-total correlation of < 0.30 confirmed the decision to exclude these five items from the proposed new instrument.

4.2.7. Principal Components Analysis, AWQ

The ten items of the AWQ were subjected to PCA using SPSS. Prior to performing the PCA, the suitability of data for factor analysis was assessed. Data were normally distributed and inspection of the correlation matrix revealed the presence of coefficients ≥ 0.30. No outliers were identified. The Kaiser-Meyer-Olkin value was 0.88, exceeding the recommended value of 0.60 (Kaiser, 1974) and Bartlett's Test of Sphericity (Bartlett, 1954) reached statistical significance, supporting the factorability of the correlation matrix.

4.2.8. Rotation, AWQ

Exploratory rotation of the 10 AWQ items was carried out to identify relationships between factor scores. Two components were revealed showing only a modest correlation between the two component scores (r = 0.22). Both varimax and oblique rotation were performed and both yielded identical results. Therefore, an oblique rotation of items was applied to the unrotated factor matrix to provide a maximally interpretable solution and for consistency with the analysis of ASSA items. A cut-off score of 0.30 was used for item loading.

PCA analysis revealed two components with eigenvalues exceeding 1. The rotated solution (see **Table 4.4**) showed a number of strong loadings with all items loading substantially on only one component. All items were assigned to a factor and the items defining each factor met simple-structure criteria (Thurstone, 1947;

Kline, 1998). The two-component solution explained 67.2% of the variance, with the first component contributing 53.9% (eigenvalue = 5.39) and the second component contributing 13.3% (eigenvalue = 1.33). Rotation converged in three iterations.

Table 4.4 Pattern matrix, AWQ

Item	Component 1	Component 2
Anxiety	0.91	
Agitation	0.90	
Anhedonia	0.87	
Dysphoria	0.87	
Amphetamine craving	0.78	
Motor retardation	0.76	
Fatigue	0.68	
Vivid, unpleasant dreams	0.63	
Increased appetite		0.88
Increased sleep		0.77

Most items loaded on the first component while only two items (appetite and sleep) loaded on the second. The loading of the item measuring increased appetite on the weaker factor together with an item-total correlation of < 0.30 confirmed the decision to exclude this item from the proposed new instrument.

4.2.9. Composition and design of the new instrument

Reliability analysis of both instruments had indicated that 9/10 items from the AWQ and 13/18 items from the ASSA met the criterion for retention to form the basis of a new instrument (see **Table 4.5**).

Table 4.5 Items retained for the new instrument

Number	Item	Original source of item
1	Poor concentration	ASSA
2	Hypersomnia	AWQ, ASSA
3	Tension	ASSA
4	Vivid, unpleasant dreams	AWQ
5	Irritability	ASSA
6	Fatigue	AWQ, ASSA
7	Agitation	AWQ
8	Suicidal ideation	ASSA
9	Inactivity	ASSA
10	Anxiety	AWQ, ASSA
11	Anhedonia	AWQ, ASSA
12	Paranoid ideation	ASSA
13	Dysphoria	AWQ, ASSA
14	Motor retardation	AWQ
15	Craving frequency	ASSA
16	Craving intensity	AWQ, ASSA

After the removal of six duplicated items, 16 items remained for inclusion in the proposed new instrument. The design and response set for the new questionnaire was based on the Subjective Opiate Withdrawal Scale (Handelsman *et al.*, 1987).

Given that amphetamine withdrawal symptoms are largely subjective, the new instrument was designed to be self-completed. Having a self-completed design removed any bias associated with inter-rater variability and was convenient for

clinical use. The scale was also designed to be suitable for once a day administration as the time frame referred to the previous 24-hour period.

Items on the new instrument were scored on a 5-point scale: 0 = Not at all; 1 = A little; 2 = Moderately; 3 = Quite a lot and 4 = Extremely. The possible range of scores, 0 – 64, higher numbers indicated greater severity. See **Appendix 4** for a copy of the new instrument, the Amphetamine Cessation Symptom Assessment (ACSA). The following section will outline the procedure used to establish the validity, reliability and factor structure of the ACSA.

4.3. Section 2: Psychometric testing of the ACSA scale

Having developed the new instrument, it was necessary to test the ACSA on a new study sample in accordance with guidelines (iv) and (v) described in **Section 4.1.2 above**.

4.3.1. Study design

Cross sectional, repeated measures design.

4.3.2. Study setting

Psychometric testing of the ACSA scale took place in the same setting as for the Australian withdrawal study described in **Chapter 2**. The study was conducted at Warinilla Clinic, a publicly funded substance use facility administered by Drug and Alcohol Services South Australia (DASSA) and located in metropolitan Adelaide, South Australia. This substance use facility includes a pharmacotherapies unit (including a pharmacy), an outpatient clinic, an assessment unit and a 12 bed inpatient unit. Subjects in the study were drawn from the inpatient population of this clinic. Treatment is provided free of charge to all clients.

4.3.3. Timeframe of data collection

Data collection took place between August 2003 and April 2005.

4.3.4. Ethical considerations

Ethical approval for the study was provided by the Ethics Committee of the Royal Adelaide Hospital in South Australia.

4.3.5. Sample size

While a wide range of sample sizes have been suggested for factor analysis, It is generally agreed that when designing trials of new instruments and particularly when factor analysis is used, bigger is better in terms of sample size (Kline, 1998; Tabachnick & Fidell, 2001; Kline, 2002). One suggestion is that in questionnaire construction, a minimum of five subjects should be tested for each questionnaire item (Feinstein, 1987). Following this recommendation, a sample size of 80 (5 x 16 ACSA items) would be the minimum needed to test the 16 item ACSA. However, others have suggested a minimum of 100 subjects (Norman & Steiner, 1994). In the present study, 107 subjects provided a total of 302 questionnaires for analysis.

Of these 107 subjects, 69 completed the ACSA on one occasion only. A subset of 38 inpatients was monitored daily for up to 13 days during which they received inpatient treatment as usual. The predictive validity of the ACSA was estimated by comparing withdrawal severity between treatment completers and treatment drop outs from this subset of 38 subjects.

4.3.6. Clinic medication protocols

The same medication protocol was used in the present study and that reported in Chapter 2. In the clinic where these studies were conducted, the standard treatment for amphetamine withdrawal involved the administration of benzodiazepines and anti-psychotics as needed in response to symptom presentation. Non-opioid analgesics were administered for pain (see **Section 2.2.11.1 above**).

4.3.7. Study subjects

Consecutive clients presenting to Drug and Alcohol Services South Australia Warinilla campus for treatment of amphetamine dependence were assessed for

consistency with the study criteria. Subjects did not receive payment for their participation in this study.

4.3.8. Study criteria

4.3.8.1. Inclusion criteria

4.3.8.1.1. Aged 18 – 65 years

4.3.8.1.2. Fulfils the DSM-IV criteria for amphetamine dependence (DSM-IV-TR, 2000)

4.3.8.1.3. Used amphetamines for at least three days a week over the previous month

4.3.8.1.4. Used amphetamines within the previous seven days

4.3.8.2. Exclusion criteria

4.3.8.2.1. Concurrent acute medical or psychiatric illness requiring acute care hospitalisation

4.3.8.2.2. Inability or unwillingness to consent to participation in the study

4.3.8.2.3. Fulfils the DSM-IV diagnostic criteria for other substance dependence, except cannabis and/or nicotine

4.3.9. Study instruments

Study instruments and methodology were the same as that used in the previous withdrawal studies. See **Section 2.2.8 above**, for a full description of study instruments.

4.3.9.1. Instruments administered on enrolment

4.3.9.1.1. Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1997) (Modules for amphetamine and other substance dependence)

4.3.9.1.2. Structured interview schedule (developed for use in this series of studies)

4.3.9.1.3. The Severity of Dependence Scale (SDS) (Gossop *et al.*, 1995)

4.3.9.2. Instruments administered on enrolment and daily for a subset of 38 subjects

The following instruments were administered on study enrolment and daily during days 0 – 12 of abstinence in a subset of 38 inpatients.

4.3.9.2.1. Amphetamine Withdrawal Questionnaire (AWQ) (Srisurapanont *et al.*, 1999)

4.3.9.2.2. The Amphetamine Cessation Symptom Assessment (ACSA) scale (scale to be validated)

4.3.9.2.3. St Mary's Hospital Sleep Questionnaire (SMHSQ) (Ellis *et al.*, 1981)

4.3.9.2.4. Clinical Global Impression (CGI) (Guy, 1976)

4.3.9.2.5. Visual Analogue Scale 'Feels unwell' – 'Feels well'

Nursing staff also recorded the radial pulse and blood pressure daily for each subject.

4.3.10. Data collection and collation

Of 107 subjects, 69 completed the ACSA on one occasion only and prior to the commencement of treatment. A subset of 38 inpatients was monitored daily for up to 13 days during which they received inpatient treatment as usual. These 107 subjects provided a total of 302 self-completed instruments during days 0 – 12 of amphetamine abstinence: 32 on day 0; 33 on day 1; 39 on day 2; 31 on day 3; 33 on day 4; 30 on day 5; 25 on day 6; 21 on day 7; 20 on day 8; 16 on day 9; 10 on day 10 and 6 on days 11 and 12 of abstinence.

At the time of data collection, the usual length of stay in the inpatient unit for medical treatment of acute amphetamine withdrawal was 7 – 10 days. However, for some subjects, the inpatient stay was extended for various reasons including lack of accommodation, timely transfer to long-term rehabilitation or because of residual symptoms. Therefore, data were collected for up to the first twelve days of abstinence after which numbers were too low for statistical tests. Questionnaires (i.e. AWQ, ACSA, SMHSQ and the CGI) were completed once daily and data collated according to the (self-reported) time since last use. That is, data collected within 24 hours of the last use of amphetamines were designated 'Day 0'; data collected 24 – 48 hours following the last use of amphetamines were designated 'Day 1' etc. Thus the maximum number of data collection days for individual subjects was 13 (days 0 – 12).

4.3.11. Data analyses

4.3.11.1. Reliability

Reliability analysis with Cronbach's alpha was performed to provide an overall estimate of internal consistency. Cronbach's alpha provides an indication of the extent to which the instrument is measuring what it is supposed to be measuring i.e., an amphetamine withdrawal syndrome. Reliability analysis also identified the degree to which individual items contributed to the measurement of the construct.

4.3.11.2. Validity

Content validity has already been established through the adoption of items from validated instruments such as the AWQ and the CSSA (Straub, 1989). Criterion-related validity was measured by assessing validity coefficients between the ACSA and criteria such as the frequency and amount of amphetamine use, length of regular amphetamine use and level of dependence. That is, it is anticipated that withdrawal symptoms will be higher in subjects who use larger amounts of amphetamines. Discriminant validity will be demonstrated if the ACSA can reliably discriminate between subjects with greater intensity of use from those whose amphetamine use is at relatively lower levels of intensity.

A high correlation between the new scale and an established scale, the AWQ, will provide further evidence of validity. A positive correlation of ≥ 0.70 between the new instrument and an established one such as the AWQ is regarded as good evidence for concurrent validity (Kline, 1998). Further evidence of convergence will be provided by examining the relationship between scores on the self-reported ACSA scale and alternative measures of withdrawal severity such as the observer-rated CGI (Foster & Cone, 1995).

4.3.11.3. Factor Analyses

The internal structure of the ACSA was analysed with Principal Components Analyses (PCA), a data reduction technique used to define linear combinations of related items. Exploratory factor analysis with oblique rotation was used to identify separate scale components and their contribution to the score variance. These separate scale components or factors then serve as subscales for the instrument (Floyd & Widaman, 1995). SPSS Version 13 was used for all data analyses.

4.3.12. Procedure

4.3.12.1. Screening and enrolment

Clients who presented to DASSA units for treatment of amphetamine dependence were screened by DASSA clinicians for basic inclusion criteria (i.e., aged 18 or over; not suffering from an acute medical or psychiatric condition requiring acute care). Clients identified as potential participants in the study were provided with a copy of the study information sheet and consent form and given a brief verbal explanation of the study requirements.

Potential subjects were then interviewed by a member of the research team to provide further information and answer any questions regarding the study. Dependence on amphetamine and other psychoactive substances were assessed using DSM-IV criteria. Clients who were assessed as dependent on amphetamine and not dependent on any other psychoactive substance (with the exception of nicotine and/or cannabis) were invited to participate in the study. Informed consent was obtained following a full explanation of the requirement of the study. Study subjects retained a copy of the information sheet and consent form.

4.3.12.2. Data collection

Following the informed consent procedure, subjects provided demographic data and a drug use history, particularly use in the 30 days prior to admission for treatment. Subjects then completed the five-item Severity of Dependence Scale, 16-item ACSA, the 10-item AWQ and the single item visual analogue scale measuring general well being. The attending clinician was asked to complete the single item Clinical Global Impressions (CGI) scale to provide an observer-rated measure of withdrawal.

4.4. Results

The final sample comprised 107 subjects who met the inclusion criteria for the study.

4.4.1. Characteristics of the study sample

Table 4.6 shows the characteristics of the study sample. Sample characteristics were similar to those observed for the first Australian withdrawal study reported in **Chapter 2**. Subjects were aged around 30 and were predominantly unemployed and single. Over half had previously received treatment for amphetamine dependence and were predominantly long-term, high-dose, severely dependent amphetamine users. Subjects were predominantly amphetamine injectors. Almost all (101/94%), reported injection as the main current route of administration. Only four had been using the oral route and one subject had either smoked or snorted amphetamines during the month prior to study enrolment.

Table 4.6 Characteristics of the study sample

Characteristics	**(*n* = 107)**
Age; mean years (SEM, range)	30.7 (0.53, 19 – 45)
Male *n* (%)	58 (54)
Unemployed *n* (%)	82 (77)
Married/cohabiting *n* (%)	25 (23)
Education, mean years (SEM, range)	10.5 (0.12, 7 – 14)
Age first used amphetamine; median years (range)	18 (12 – 38)
Length of regular amphetamine use; mean years (SEM, range)	10.4 (0.57, 1 – 25)
Days of amphetamine use in the previous month; mean (SEM, range)	21.7 (0.64, 12 – 30)
Used every day in the previous month; *n* (%)	32 (30)
Amount (AUD$) spent per day on amphetamine; median (range)	150 (25 – 850)
Grams used, per day of use, in previous month; median (range)	0.65 (0.1 – 6.5)
Total grams used during previous month; median (range)	12.8 (1.2 – 168)
Severity of Dependence; median (range)	10.4 (0 – 15)
Previously treated for amphetamine dependence; *n* (%)	53 (50)

4.4.2. Endorsement rates for ACSA items

Table 4.7 shows the endorsement rates for individual ACSA items. Endorsement rates are the percentage of times that a score above zero was given for that item. Tension, fatigue, anxiety, agitation and irritability were the most frequently endorsed items over the first 13 days of abstinence while the item with the lowest rate of endorsement – suicidal ideation was endorsed just over half of the time.

Table 4.7 Endorsement rates for ACSA items

ACSA Item	Percentage endorsement
Tension	94.7
Fatigue	94.0
Anxiety	93.0
Agitation	92.7
Irritability	91.7
Paranoid Ideation	89.7
Hypersomnia	89.7
Inactivity	88.1
Craving frequency	88.1
Anhedonia	87.7
Craving intensity	87.1
Depression	87.1
Poor concentration	85.8
Motor retardation	74.8
Vivid, unpleasant dreams	64.6
Suicidal Ideation	53.6

4.4.3. Reliability analysis: ACSA items

Reliability analysis with Cronbach's alpha was performed to provide an overall estimate of internal consistency. Cronbach's alpha was satisfactory at 0.76. Corrected item-total correlations ranged from 0.42 for vivid, unpleasant dreams to 0.81 for anxiety (see **Table 4.8**). While a satisfactory coefficient alpha is indicative of scale unidimensionality it is important to check this assumption by further analysis with another technique such as principal components analysis (Smith & McCarthy, 1995).

Table 4.8 Corrected item-total correlations for ACSA items

Item	Corrected item-total correlations
Anxiety	0.81
Agitation	0.80
Tension	0.80
Irritability	0.78
Poor concentration	0.73
Anhedonia	0.73
Depression	0.71
Craving frequency	0.68
Craving intensity	0.67
Paranoid Ideation	0.63
Motor retardation	0.59
Suicidal Ideation	0.58
Fatigue	0.57
Inactivity	0.53
Hypersomnia	0.44
Vivid, unpleasant dreams	0.42

4.4.4. Principal Components Analysis

The 16 items of the ACSA scale were subjected to PCA using SPSS. Prior to performing the PCA, the suitability of data for factor analysis was assessed. A correlation matrix derived from the data identified a number of coefficients of 0.30 and over. Distributions of aggregate ACSA and individual item scores were normal and no outliers were identified. The Kaiser-Meyer-Olkin value was 0.89, exceeding the recommended value of 0.60 (Kaiser, 1974) and the Bartlett's Test of Sphericity (Bartlett, 1954) reached statistical significance, supporting the factorability of the correlation matrix. Only variables with loadings of 0.30 and above were included

as loadings of < 0.30 account for less than 9% of the variance and contribute little to the factor (Tabachnick & Fidell, 2001; Kline, 2002). Principal components analysis revealed the presence of three components with eigenvalues exceeding 1.

4.4.5. Rotation, ACSA

A factor score correlation of > 0.30 has been suggested as the cut off point for choosing between orthogonal or oblique rotation methods (Tabachnick & Fidell, 2001).

Table 4.9 Pattern Matrix

	Component		
	1	2	3
Item	**Anxiety/Craving**	**Hypersomnia**	**Depression**
Craving frequency	0.93		
Craving intensity	0.90		
Irritability	0.71		
Tension	0.70		
Agitation	0.70		
Anxiety	0.68		
Vivid dreams	0.43		
Hypersomnia		0.86	
Fatigue		0.81	
Suicidal Ideation			-0.78
Anhedonia			-0.77
Depression			-0.72
Paranoid Ideation			-0.66
Poor concentration			-0.61
Inactivity		0.33	-0.54
Motor retardation		0.36	-0.53

As correlations between factor scores in the present data set ranged between 0.29 and -0.57, oblique rotation was selected as the appropriate technique to apply to the three factor solution (see **Table 4.9**). A cut off of 0.30 was used for item loading and components interpreted via the pattern matrix. The rotated factor solution explained a total of 64.5% of the variance with component 1 contributing 48% (eigenvalue = 7.7), component two contributing 8.9% (eigenvalue = 1.4) and component three contributing 7.5% (eigenvalue = 1.2). Rotation converged in eleven iterations.

4.4.6. Interpretation of factors

The greater the loading of variables onto factors or components, the more the variable is a 'pure' measure of that factor (Tabachnick & Fidell, 2001). In the present analysis, all items loaded onto at least one component. With the exception of inactivity and motor retardation, the items defining each factor met simple-structure criteria (at least 0.30 on a home factor and < 0.30 on all other factors) (Thurstone, 1947; Kline, 1998). Inactivity and motor retardation were assigned to the factor on which they had loaded most strongly i.e., component three.

The three factors derived from the rotation and their constituent items were as follows. The first factor was labelled **'Anxiety and Craving'** and was defined by seven items: craving frequency and intensity, agitation, irritability, tension, anxiety and vivid, unpleasant dreams. This was the strongest component, contributing 48% of the variance in the scale. Two of the loadings on this factor, craving frequency and intensity, were in excess of 0.71 (50% of overlapping variance) which is considered 'excellent' (Comrey & Lee, 1992). Four other items loading on this factor, irritability, agitation, tension, anxiety, were in excess of 0.63 (40% overlapping variance) which is considered 'very good'. Only vivid dreams showed a relatively weak loading of 0.43 on this factor (Comrey & Lee, 1992).

The second factor was labelled **'Hypersomnia'** and defined by two items: hypersomnia and fatigue. Both of these items loaded strongly and exclusively on this component.

The third factor was labelled **'Depression'** and was defined by seven items: suicidal ideation, anhedonia, depression, paranoid ideation, poor concentration,

inactivity and motor retardation. Of these seven items, suicidal ideation, anhedonia and depression loaded strongly (50% overlapping variance). Paranoid ideation showed a 'very good' loading (40% overlapping variance). Poor concentration was considered 'good' (30% overlapping variance) while the loadings of inactivity and motor retardation were considered 'fair' (20% overlapping variance) (Comrey & Lee, 1992).

Analogue factor scores were then computed for each factor by summing the actual values of the ACSA items loading on each factor. Reliability analysis was conducted for the three scale components.

4.4.7. Reliability analysis: Anxiety and Craving component

Cronbach's alpha for the 'Anxiety and Craving' component was satisfactory at 0.79 (see **Table 4.10**).

Table 4.10 Corrected item-total correlations: Anxiety and Craving component

ACSA item	Corrected item-total correlations
Anxiety	0.84
Agitation	0.83
Irritability	0.83
Tension	0.83
Craving intensity	0.77
Craving frequency	0.75
Vivid, unpleasant dreams	0.47

Corrected item-total correlations ranged from 0.47 for vivid, unpleasant dreams to 0.84 for anxiety

4.4.8. Reliability analysis: Hypersomnia component

Cronbach's alpha for the 'Hypersomnia' component was satisfactory at 0.90. Corrected item-total correlations were similar for both items (see **Table 4.11**).

Table 4.11 Corrected item-total correlations: Hypersomnia component

ACSA item	Corrected item-total correlations
Hypersomnia	0.85
Fatigue	0.84

4.4.9. Reliability analysis: Depression component

Cronbach's alpha for the 'Depression' component was satisfactory at 0.78.

Table 4.12 Corrected item-total correlations: Depression component

ACSA item	Corrected item-total correlations
Anhedonia	0.80
Depression	0.75
Poor concentration	0.74
Paranoid Ideation	0.67
Suicidal Ideation	0.64
Motor retardation	0.62
Inactivity	0.59

Corrected item-total correlations ranged from 0.59 for inactivity to 0.80 for anhedonia (see **Table 4.12**).

4.4.10. Correlations between aggregate ACSA and factor scores

Correlational analyses, conducted on the unweighted factor-scale scores and aggregate ACSA scores revealed significant positive correlations between all elements of the analysis (see **Table 4.13**).

Table 4.13 Correlations between aggregate ACSA and component scores

		Factor		
Scale	**ACSA**	**Anxiety/Craving**	**Hypersomnia**	**Depression**
ACSA		0.91	0.59	0.91
Anxiety/Craving	0.91		0.41	0.70
Hypersomnia	0.59	0.41		0.44
Depression	0.91	0.70	0.44	

All correlations significant at $p < 0.01$

The strong relationship between the depression-related and anxiety-related symptom clusters is consistent with the usual presentation seen in clinical cases of depression.

4.4.11. Concurrent validity

While the relationship between the ACSA and the AWQ was influenced by an overlap in items covering the same symptoms, the strong correlation between aggregate ACSA and subscale scores and the established scale provides some support for the validity of the ACSA (see **Table 4.14**). A positive correlation of ≥ 0.70 between a new instrument and an established one measuring the same construct is considered as evidence for concurrent validity (Kline, 1998).

Table 4.14 Relationship between aggregate ACSA and component scores and other measures of withdrawal severity

		Factor		
Scale	**ACSA**	**Anxiety/Craving**	**Hypersomnia**	**Depression**
AWQ	0.88	0.81	0.61	0.77
General well-being	-0.46	-0.39	-0.27	-0.44
CGI	0.31	0.32	0.15	0.26

All correlations significant at $p < 0.01$

There was a moderate negative correlation between self-reported general well-being and scores on the ACSA scale.

4.4.12. Relationship between aggregate ACSA and component scores and measures of sleep during withdrawal

The 'Anxiety and Craving' component score was associated with a reduction in the quality of several sleep characteristics while 'Hypersomnia' was associated with greater hours of sleep and lower clearheadedness on arising (see **Table 4.15**).

'Depression' was principally associated with reductions in clearheadedness on arising, sleep satisfaction and sleep quality. There were also weak but significant associations between scores on the 'Depression' component and increased sleep latency and number of awakenings during the night.

Table 4.15 Relationship between aggregate ACSA and component scores and measures of sleep during withdrawal

		Factor		
	ACSA	**Anxiety/Craving**	**Hypersomnia**	**Depression**
Day sleep	0.03	-0.03	0.40**	-0.01
Night sleep	-0.14*	-0.23**	0.17**	-0.11
Sleep latency	0.23**	0.27**	0.11	0.16*
Times awake	0.26**	0.36**	0.00	0.15*
Sleep quality	-0.33**	-0.44**	0.00	-0.21**
Sleep depth	-0.21**	-0.33**	0.01	-0.08
Clearheadedness	-0.51**	-0.45**	-0.32**	-0.48**
Sleep satisfaction	-0.42**	-0.48**	-0.06	-0.33**

* $p < 0.05$, ** $p < 0.01$

4.4.13. Criterion-related validity

Criterion-related validity was assessed by analysing the relationship between ACSA scores and measures of amphetamine dependence (see **Table 4.16**).

Table 4.16 Relationship between aggregate ACSA and component scores and measures of amphetamine dependence

		Factor		
	ACSA	**Anxiety/ Craving**	**Hypersomnia**	**Depression**
Aggregate SDS score	0.28**	0.30**	0.18**	0.20**
SDS item 1: Think use out of control	0.20**	0.21**	0.16**	0.12*
SDS item 2: Missing hit make you anxious	0.30**	0.33**	0.17**	0.20**
SDS item 3: Worry about use	0.11	0.09	0.13*	0.09
SDS item 4: Wish you could stop	0.01	0.13*	-0.02	-0.01
SDS item 5: Think stopping difficult	0.28**	0.24**	0.15**	0.27**

* $p < 0.05$, ** $p < 0.01$

There were weak to modest, but significant positive correlations between aggregate ACSA scores and measures of amphetamine dependence.

Similarly, there were modest but significant positive correlations between ACSA scores (aggregate and factor scores) and measures of recent amphetamine use (see **Table 4.17**).

Table 4.17 Relationship between aggregate ACSA and component scores and measures of recent amphetamine use

		Factor		
Amphetamine use in previous month	**ACSA**	**Anxiety/Craving**	**Hypersomnia**	**Depression**
Days used	0.21**	0.22**	0.13*	0.16**
Total grams used	0.25**	0.22**	0.17**	0.22**
Cost per day	0.21**	0.21**	0.16**	0.17**

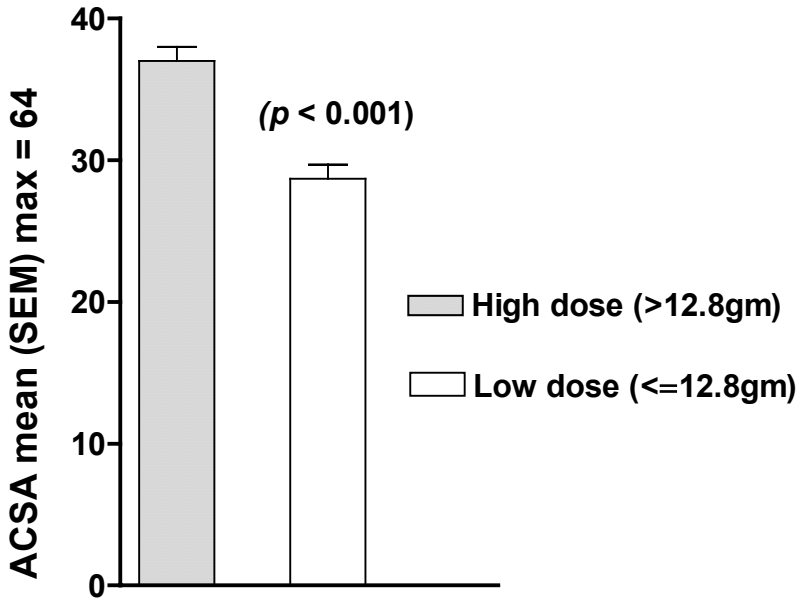
$p < 0.05$ ** $p < 0.01$

4.4.14. Discriminant validity

The ACSA reliably discriminated between subjects with greater intensity of use and those whose amphetamine use was at relatively lower levels. An index variable was created by multiplying the number of days of amphetamine use in the month prior to admission for treatment and the amount used on each day. This variable provided a measurement of the total weight (in grams) of amphetamine used in the previous month (median = 12.8, range 1.2 – 168) gm. A median split was performed on the index variable, as the amount of amphetamine used in the previous month was not normally distributed. Subjects using ≤ 12.8 gm in the month prior to treatment were designated a 'low dose' group while those using > 12.8 gm were designated a 'high dose' group (see **Figure 4.1**).

Subjects who had used ≤ 12.8 gm of amphetamine during the month prior to treatment entry had significantly lower ACSA scores (mean = 28.7, SEM = 1.0) in comparison to those using > 12.8 gm amphetamine (mean = 37.0, SEM = 1.0, $t = 5.52$, df = 298 $p < 0.001$).

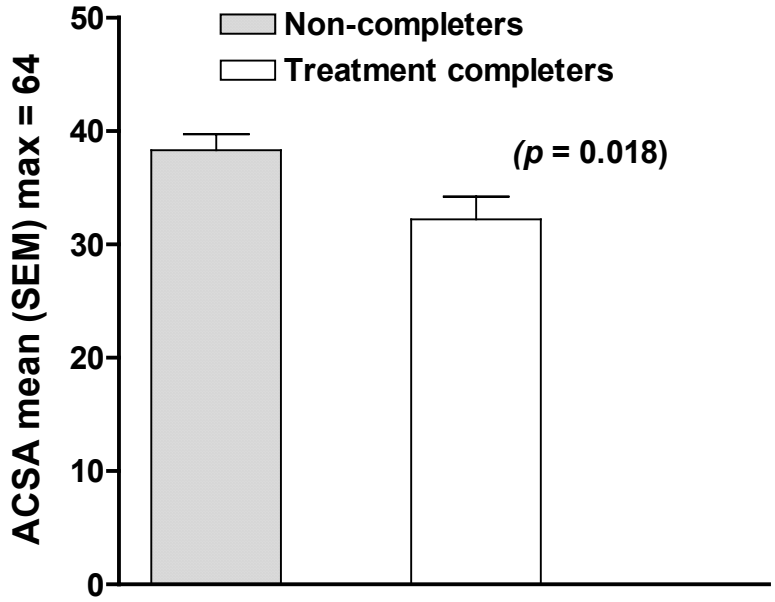
Figure 4.1 Comparison of ACSA scores for 'low' and 'high' dose users



4.4.15. Predictive validity

To assess the predictive validity of the ACSA, a subset (*n* = 38) of the total sample (*n* = 107) were monitored daily during inpatient treatment for amphetamine withdrawal (see **Figure 4.2**). These 38 subjects received the treatment that is normally given to inpatients undergoing amphetamine withdrawal treatment. Only data from the first 0 – 4 days of abstinence was used (102 ACSA questionnaires). This was done for two reasons. Firstly, fewer subjects from the non-completers group were, by definition, available for assessment over the later study days – secondly, withdrawal severity declined over time in subjects who remained in treatment.

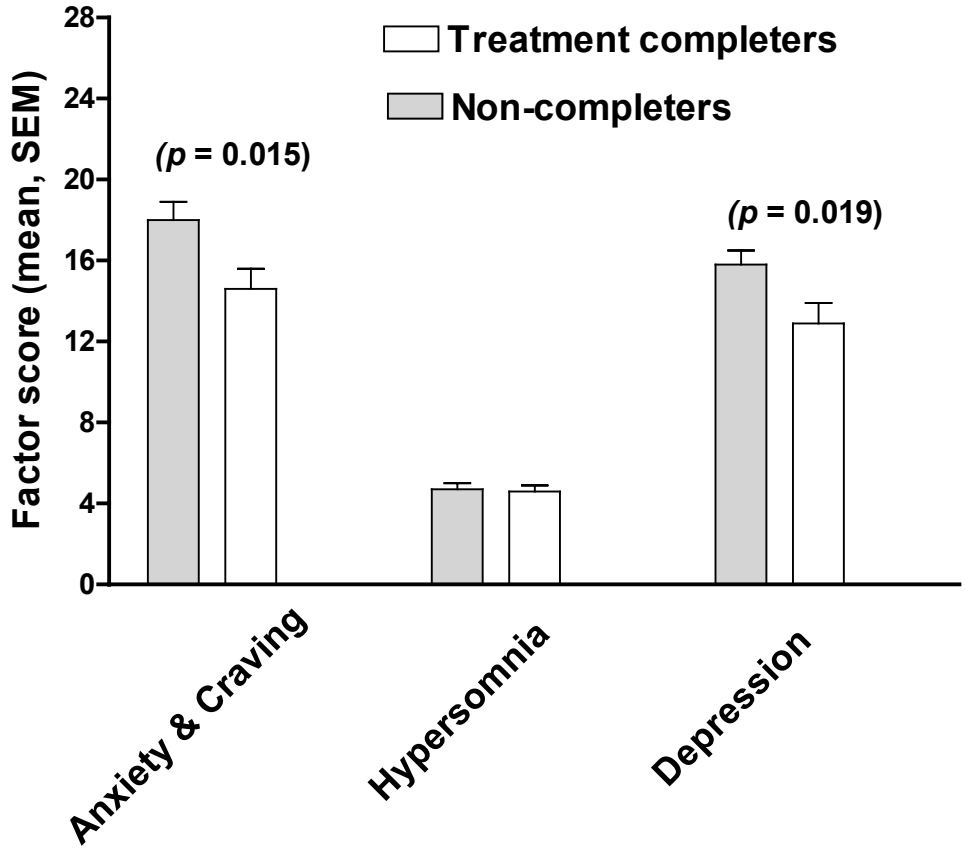
Figure 4.2 Comparison of ACSA scores for treatment completers and non-completers



Treatment completers had significantly lower ACSA scores (mean = 32.2, SEM = 2.0) in comparison to those who left treatment early (mean = 38.3, SEM = 1.4, t = 2.4, df = 88 p = 0.018) during the first 0 – 4 days of abstinence.

During the first 0 – 4 days of abstinence, treatment completers had significantly lower 'Anxiety and Craving' scores (mean = 14.6, SEM = 1.0) in comparison to those who left treatment early (mean = 18.0, SEM = 0.9, t = 2.4, df = 100 p = 0.015). Similarly, treatment completers had significantly lower 'Depression' scores (mean = 12.9, SEM = 1.0) in comparison to non-completers (mean = 15.8, SEM = 0.7, t = 2.4, df = 89 p = 0.019) see **Figure 4.3**. Of the three subscales, only 'Hypersomnia' did not show predictive validity (p = 0.9).

Figure 4.3 Comparison of ACSA subscale scores for treatment completers and non-completers



4.5. Discussion

The Amphetamine Cessation Symptom Assessment scale is a reliable and valid instrument for the measurement of amphetamine withdrawal symptoms in newly abstinent amphetamine users. The development of the ACSA was based on two existing scales of known reliability and validity, the AWQ (Srisurapanont *et al.*, 1999) and a form of the CSSA modified for use with amphetamine users (Kampman *et al.*, 1998). In the preliminary studies of newly abstinent inpatients (see **Chapters 2** and **3**), the CSSA (renamed the ASSA) was modified for use with amphetamine users and completed daily, together with the AWQ, for one to three weeks of abstinence. Subsequent reliability and principal components analysis of data from the AWQ and the ASSA facilitated item selection leading to the exclusion of five items from the ASSA and one from the AWQ.

After the removal of duplicated items, 16 items were incorporated into the new instrument – the Amphetamine Cessation Symptom Assessment (ACSA) scale. The response format and design for the ACSA was based on an established opiate withdrawal instrument, the Subjective Opiate Withdrawal Scale (Handelsman *et al.*, 1987). As amphetamine withdrawal symptoms are largely subjective, the ACSA was designed to be self-completed, thereby avoiding any bias associated with inter-rater variability. The scale time frame referred to the previous 24-hour period, making the scale suitable for once a day administration and convenient for clinical use and research purposes. Therefore, the new scale was designed to maximise both efficiency and reliability by retaining the minimum number of items consistent with the accurate measurement of the construct, i.e. amphetamine withdrawal (Smith & McCarthy, 1995).

The work in the second section of this chapter demonstrated that the structure of the ACSA could be clarified through psychometric analysis. Content validity for the new instrument had already been established through the adoption of items from validated instruments such as the AWQ and the CSSA (Straub, 1989). The suitability of the new instrument for use in amphetamine withdrawal was confirmed by the high rate of endorsement observed. Endorsement rates for the 16 ACSA items were uniformly high. Questions relating to tension, fatigue, anxiety, agitation and irritability were the most frequently endorsed items – a finding consistent with clinical observations of patients undergoing amphetamine withdrawal.

Reliability analysis indicated a satisfactory level of internal consistency for the ACSA that was suggestive of unidimensionality. However, a principal components analysis followed by oblique rotation showed that amphetamine withdrawal was not unidimensional and that a three-factor solution provided a good fit to the data with all items being assigned to a factor. The strongest factor, comprising seven items, was labelled ‘Anxiety and Craving’. Items loading on this factor included craving frequency and intensity, agitation, irritability, tension, anxiety and vivid, unpleasant dreams. The second component, ‘Hypersomnia’ comprised fatigue and hypersomnia items and the third factor labelled ‘Depression’ comprised seven items assessing suicidal ideation, anhedonia, depression, paranoid ideation, poor concentration, inactivity and motor retardation.

Analogue factor scores were computed for each factor by summing the actual values of the ACSA items loading on each factor. This technique has the advantage of producing scores that can be calculated easily by clinicians and is justifiable in terms of the structure exhibited in the factor analysis. Reliability analysis for the three scale components was satisfactory suggesting that the three components were each unidimensional and could function as subscales of the ACSA.

The strong positive correlation between the new instrument and an established one (the AWQ) provided evidence for concurrent validity (Kline, 1998). Further evidence of convergence was provided by the modest but significant positive relationship between the ACSA and an alternative method of evaluating the same construct such as observer-rated withdrawal severity (Foster & Cone, 1995).

Positive relationships between the ACSA (aggregate and subscale scores) and criteria such as the number of days on which amphetamine had been used, total grams used and the amount of money spent on amphetamine per day in the month prior to admission provided evidence of criterion-related validity. Further evidence of criterion-related validity was provided by the positive relationship between the ACSA (aggregate and subscale scores) and the level of amphetamine dependence. The relationship between withdrawal severity and amphetamine dependence was mediated largely by concordance between ACSA scores and two SDS items, namely, ‘did the prospect of missing a dose make you very anxious or worried? (e.g. going without amphetamine)’ and ‘how difficult would you find it to stop or go without?’. This finding suggests that amphetamine users who anticipate difficulty in achieving abstinence and who become anxious when contemplating the absence of amphetamine experience a more severe withdrawal course.

The ACSA reliably discriminated between subjects with greater intensity of use from those whose amphetamine use was at relatively lower levels. As anticipated, withdrawal symptoms were higher in subjects who had used larger amounts of amphetamine in the month prior to treatment entry. The predictive validity of the ACSA was assessed by comparing withdrawal severity between subjects who completed treatment with those who did not. To this end, a subset of the total

sample was monitored daily during inpatient treatment for amphetamine withdrawal. Only data from the first 0 – 4 days of abstinence was used. This was done for two reasons. Firstly, fewer subjects from the non-completers group were, by definition, available for assessment over the later study days. Secondly, withdrawal severity declined over time in subjects who remained in treatment. Treatment completers had significantly lower ACSA scores in comparison to those who left treatment early. Comparison of factor scores during the first 0 – 4 days of abstinence showed that treatment completers had significantly lower 'Anxiety and Craving' and 'Depression' subscale scores in comparison to non-completers. Of the three subscales, only 'Hypersomnia' did not show predictive validity. This finding suggests that affective and mood related symptoms are more likely to lead to treatment drop out than fatigue and sleep related symptoms in patients undergoing amphetamine withdrawal treatment.

Higher total ACSA and 'Anxiety and Craving' scores were associated with a reduction in the quality of several sleep characteristics. Specifically, greater sleep latency and night time awakenings, reduced hours of sleep during the night, reduced sleep quality, depth, satisfaction and reduced clearheadedness on awakening. As expected, higher scores for the 'Hypersomnia' subscale were associated with greater hours of sleep and less clearheadedness on arising. Higher 'Depression' scores were associated with reductions in clearheadedness on arising, sleep satisfaction and sleep quality as well as increased sleep latency and number of awakenings during the night.

The three factor structure found in the original study of the AWQ by Srisurapanont and colleagues (Srisurapanont *et al.*, 1999) was not replicated in the data set analysed in **Section 4.2 above**. There may be several reasons for this lack of replication. Firstly, the original AWQ study measured withdrawal severity in Thai amphetamine users of around 20 years of age who had been either swallowing or smoking amphetamines for around two years. All were currently undergoing inpatient amphetamine withdrawal treatment and all had been abstinent from amphetamines for between one and five days. In contrast, the present data set included a broader range of subjects, many of whom had administered

amphetamines by injection, were older and had been using amphetamines longer, all of which may have influenced the factor loadings of the AWQ.

4.5.1. Limitations of the study

For the present study, 107 subjects provided a total of 302 questionnaires for analysis. This sample size is considered adequate to test a 16 item instrument (Feinstein, 1987) and complies with the minimum sample size requirement of 100 subjects when testing a new instrument (Norman & Steiner, 1994). However, when conducting a psychometric evaluation of a new instrument, particularly where factor analysis is used, bigger is always considered better in terms of sample size (Kline, 1998; Tabachnick & Fidell, 2001; Kline, 2002). A replication of the ACSA factor structure in a larger sample would provide confirmation of the psychometric structure revealed in the present analysis.

4.5.2. Summary and conclusions

The ACSA has shown satisfactory reliability and a clear psychometric structure, delineating symptom clusters and their correlates with a three factor solution providing the best fit to the data. Furthermore, using a number of indices, the three components also exhibited satisfactory reliability and validity. These results indicate that the ACSA could play an important role in providing clinical outcome data, particularly in testing and outcome evaluation of interventions into amphetamine withdrawal and in guiding the development of new treatment protocols.

An edited version of this chapter has been submitted for peer review.

5. CHAPTER 5: OPEN LABEL TRIALS OF MIRTAZAPINE AND MODAFINIL IN AMPHETAMINE WITHDRAWAL

5.1. Introduction

Reviews of opioid drug dependence treatment have indicated that effective pharmacotherapies can attract and retain users in treatment with consequent benefits in terms of reduced illicit drug use and increased health and psychosocial functioning (Gowing *et al.*, 2001). However, the absence of empirical evidence on which to base effective pharmacological protocols for amphetamine withdrawal treatment may result in the application and delivery of treatments, which may or may not be effective.

Current pharmacological treatment approaches to the management of amphetamine withdrawal and dependence include the use of benzodiazepines, antipsychotics and/or antidepressants in combination with symptomatic medications. The lack of established treatment protocols was highlighted by an exhaustive review of the literature that failed to identify studies describing the natural history of amphetamine withdrawal phenomena or effective pharmacotherapies (Jenner & Saunders, 2004). Failure to manage amphetamine withdrawal symptoms during treatment may contribute to the high rates of relapse in the first days or weeks post cessation (Brecht *et al.*, 2000) and identification of an effective pharmacotherapy for amphetamine dependence and amelioration of withdrawal symptoms would be of considerable value both to patients and to their treating clinicians.

Chapters 2 and **3** described the first systematic examination of the time course and severity of a range of symptoms emerging during the first one – three weeks of amphetamine abstinence (McGregor *et al.*, 2003, 2003, 2005). As a consequence of these studies, an amphetamine withdrawal syndrome that can be categorised into two phases was identified. The initial or acute phase lasted for 7 – 10 days, during which overall symptom severity declined in a linear pattern from a high initial peak. The second, or sub-acute phase lasted at least a further two weeks during which symptoms remained relatively mild and stable. Additionally, three clusters of symptoms that patients typically experience during the acute

phase of amphetamine withdrawal were identified by factor analysis: anxiety/craving, hypersomnia/fatigue and depression/anhedonia (McGregor, Srisurapanont, Mitchell & White, 2004). These preliminary studies provided valuable information allowing for the targeting of specific withdrawal symptoms at specific times during the early phase of amphetamine abstinence. Having developed and tested an empirically-derived tool for the measurement of amphetamine withdrawal symptoms, the next step was to identify potentially effective pharmacotherapies for amphetamine withdrawal treatment.

5.1.1. Identification of potential pharmacotherapies for amphetamine withdrawal treatment

The identification of pharmacotherapies with potential utility in amphetamine withdrawal was based on two approaches. Firstly, an approach based on the neurotransmitter deficit model (see **Section 1.15 above**) guided the focus towards medications with the potential to raise synaptic concentrations of one or more of the three neurotransmitters impacted by amphetamine – dopamine, serotonin and noradrenaline. However, while dopamine agonists have not been studied in amphetamine dependence, studies of direct and indirect dopamine agonists in another psychostimulant (cocaine) using group have been generally disappointing (for review see Kosten *et al.*, 2002). Consequently, the focus of inquiry shifted to the other two neurotransmitters – serotonin and noradrenaline. Newer antidepressants with a dual action and a rapid onset of action such as mirtazapine and venlafaxine were investigated. Of these, mirtazapine had the greater serotonergic effects, in addition to its noradrenergic effects and was thus considered likely to have a greater impact on both noradrenaline and serotonin concentrations.

5.1.2. Mirtazapine

Mirtazapine is approved in Australia for the treatment of major depression. It is manufactured by Organon under the trade name of Avanza ®. Mirtazapine has approval status in the UK, Republic of Ireland, Germany, Austria, France, Greece, Turkey, Italy, Portugal, Spain, Netherlands, Denmark, Finland, Sweden, Brazil, Chile, Hong Kong, Singapore, Ecuador, Peru and the United States for the

treatment of depression. The recommended dosage for treatment of depression in adults is initially 15 mg daily before bed, followed by dose increases (usually 30 – 45 mg, up to 60 mg) daily.

5.1.2.1. Mirtazapine: mechanism of action

The noradrenergic and serotonergic antidepressant, mirtazapine, enhances noradrenergic transmission by blocking the alpha 2-adrenoceptors (de Boer, 1996; de Boer, Nefkens, van Helvoirt & van Delft, 1996). Mirtazapine also enhances serotonergic transmission indirectly via noradrenergic stimulation of alpha 1-adrenoceptors and blockade of alpha 2-heteroreceptors (De Montigny, Haddjeri, Mongeau & Blier, 1995; Haddjeri, Blier & de Montigny, 1995). Serotonergic stimulation is mediated largely by the 5-HT1 receptor as mirtazapine blocks both 5-HT2 and 5-HT3 receptors. Therefore, the antidepressant effect of mirtazapine is thought to be mediated by a combination of postsynaptic noradrenaline and 5-HT1 receptor stimulation. Importantly, the action of mirtazapine in blocking both 5-HT2 and 5-HT3 receptors is thought to be associated with its efficacy and tolerability. That is, the 5-HT2 blocking effect is thought to contribute to the anxiolytic effects of mirtazapine and its beneficial effects on sleep. Moreover, blockade of this receptor may also prevent the agitation, restlessness and sexual dysfunction that can occur with non-specific stimulation of the serotonin system. Similarly, 5-HT3 blockade prevents nausea and vomiting and also helps to reduce headaches (Nutt, 2002). Therefore, mirtazapine augments the release of norepinephrine and 5-HT1A-mediated serotonergic transmission, a dual mode of action which may also be responsible for its rapid onset of action (Anttila & Leinonen, 2001; Blier, 2003).

5.1.2.2. Mirtazapine: pharmacokinetics

Mirtazapine is rapidly and well absorbed from the gastrointestinal tract after single and multiple oral administrations. Peak plasma concentrations are reached within 2 hours (Timmer, Sitsen & Delbressine, 2000). Mirtazapine binds to plasma proteins (85%) in a non-specific and reversible way. The absolute bioavailability is approximately 50%, mainly because of gut wall and hepatic first-pass metabolism. The presence of food has a minor effect on the rate, but does not affect the extent, of absorption. Mirtazapine shows linear pharmacokinetics over a dose range of 15

to 80mg. The elimination half-life of mirtazapine ranges from 20 to 40 hours, which is consistent with the time to reach steady state (4 – 6 days) (Timmer *et al.*, 2000; Anttila & Leinonen, 2001). Total body clearance as determined from intravenous administration to young males amounts to 31 L/h. Approximately 100% of the orally administered dose is excreted via urine and faeces within four days. Biotransformation is mainly mediated by the CYP2D6 and CYP3A4 isoenzymes. Inhibitors of these isoenzymes, such as paroxetine and fluoxetine, cause modestly increased mirtazapine plasma concentrations (17 and 32%, respectively) without leading to clinically relevant consequences (Timmer *et al.*, 2000).

5.1.2.3. Mirtazapine: safety

Mirtazapine has been shown to be safe, and well tolerated (Nutt, 2002) even during long-term use (Thompson, 1999; Blier, 2003). The most common side effects reported are dry mouth, sedation, and increases in appetite and body weight. In vitro studies suggest that mirtazapine is unlikely to cause clinically significant drug-drug interactions (Anttila & Leinonen, 2001).

5.1.2.4. Mirtazapine: efficacy

The antidepressant efficacy of mirtazapine has been established in several placebo-controlled trials (Thompson, 1999; Blier, 2003). Studies confirm that mirtazapine is well tolerated, with good efficacy, and has an earlier onset of action in comparison to SSRIs (Thompson, 1999; Benkert, Muller & Szegedi, 2002; Blier, 2003). Importantly, mirtazapine may increase serotonin concentrations early in treatment. In an animal model, mirtazapine produced an enhanced serotonin transmission after only two days of treatment (Besson, Haddjeri, Blier & de Montigny, 2000). Currently available evidence suggests that mirtazapine is effective in all levels of severity of depressive illness, as well as in a broad range of symptoms associated with depression. Further, mirtazapine may yield superior therapeutic efficacy compared to the SSRIs, particularly for difficult-to-treat patients (Gorman, 1999). Mirtazapine also appears to be useful in patients suffering from depression comorbid with anxiety symptoms and sleep disturbance (Anttila & Leinonen, 2001). Additionally, there is some evidence that mirtazapine may be useful for the treatment of nightmares (Lewis, 2002). These are important

properties in a potential treatment for amphetamine withdrawal as depression, anxiety, vivid/unpleasant dreams and sleep disturbance are major features of acute amphetamine withdrawal (McGregor *et al.*, 2003, 2003, 2005).

The second approach to the identification of pharmacotherapies with potential utility in amphetamine withdrawal focused on hypersomnolence and fatigue, both of which are prominent features of the amphetamine withdrawal syndrome. Modafinil, a medication with wake-promoting properties was identified as the medication most likely to alleviate these symptoms during amphetamine withdrawal.

5.1.3. Modafinil

Modafinil is approved in Australia for the treatment of narcolepsy. It is marketed in Australia by CSL under the trade name of Modavigil ®. Modafinil is approved in the United States, Sweden, France, Spain, Germany, Italy, Austria, Switzerland and the Netherlands to treat narcolepsy and in the UK to treat sleep apnoea/ hypopnea syndrome and narcolepsy. For the treatment of narcolepsy, the recommended dose of modafinil is 200 – 400 mg/day in the morning or divided doses, morning and noon.

5.1.3.1. Modafinil: mechanism of action

Although the mechanism of action is not clear, existing evidence points to a dopaminergic role in modafinil induced wakefulness. For example, modafinil increased extracellular dopamine concentrations in rat nucleus accumbens (Ferraro, Tanganelli, O'Connor, Antonelli, Rambert & Fuxe, 1996; Ferraro, Antonelli, O'Connor, Tanganelli, Rambert & Fuxe, 1997) while Nishino and colleagues have reported a correlation between the binding affinity at the dopamine transporter and the wake promoting action of modafinil in dogs (Nishino, Mao, Sampathkumaran & Shelton, 1998). Further, dopamine transporter knockout mice showed no wakefulness-enhancing response to modafinil, even at large doses (300 mg/kg) (Wisor, Nishino, Sora, Uhl, Mignot & Edgar, 2001). Other investigations have used Fos immunohistochemistry to identify specific brain regions activated by modafinil. Using a rat model, Scammell and colleagues found that modafinil (75 mg/kg) increased Fos immunoreactivity in the tuberomammillary

nucleus and in orexin neurons of the perifornical area, two cell groups which are thought to be involved in the regulation of wakefulness (Scammell, Estabrooke, McCarthy, Chemelli, Yanagisawa, Miller & Saper, 2000). However, in later studies, orexin null mice were found to be more responsive to the wakefulness-promoting effects of modafinil in comparison to wild-type mice (Willie, Renthal, Chemelli, Miller, Scammell, Yanagisawa & Sinton, 2005) as were orexin/ataxin-3 transgenic mice, in which orexin neurons were specifically ablated (Mieda, Willie, Hara, Sinton, Sakurai & Yanagisawa, 2004). The authors concluded that the non-selective activation on orexin neurons by modafinil was a consequence of the wakefulness induced by modafinil rather than the principal mechanism of action. As Willie and colleagues have suggested, modafinil may directly inhibit the increased drive for sleepiness that normally follows prolonged wakefulness (Willie *et al.*, 2005) such as that induced by amphetamine administration.

5.1.3.2. Modafinil: pharmacokinetics

A review of the clinical pharmacokinetic profile of modafinil showed that it is readily absorbed after oral dosing, reaching maximum plasma concentrations at 2 – 4 hours after administration and pharmacokinetic steady state within 2 – 4 days (Robertson & Hellriegel, 2003). Modafinil pharmacokinetics have been shown to be dose and time independent over the range of 200 mg to 800 mg (Wong, Simcoe, Hartman, Laughton, King, McCormick & Grebow, 1999; Robertson & Hellriegel, 2003). In these studies, steady-state pharmacokinetics of modafinil were characterised by a rapid oral absorption rate, a low plasma clearance of approximately 50 mL/min, a volume of distribution of approximately 0.8 L/kg, and a half-life of approximately 15 hours. Only two metabolites reach appreciable concentrations in plasma, i.e. acid modafinil and modafinil sulfone. Acid modafinil is the principal metabolite (40 to 50% of the dose). In preclinical models, modafinil acid, modafinil sulfone, 2-{(diphenylmethyl) sulfonyl} acetic acid and 4-hydroxy modafinil, were inactive or did not appear to mediate the arousal effects of modafinil. Modafinil is primarily eliminated via metabolism, mainly in the liver, with subsequent excretion of metabolites in the urine. Less than 10% of the dose is excreted as unchanged drug. Metabolism is largely via amide hydrolysis, with

lesser contributions from cytochrome P450 mediated oxidative pathways (Robertson & Hellriegel, 2003).

The potential for metabolic interactions between modafinil and other drugs has been the subject of review (Robertson & Hellriegel, 2003). In vitro, modafinil was observed to produce a reversible inhibition of CYP2C19 in human liver microsomes. It also caused a small, but concentration-dependent, induction of CYP1A2, CYP2B6 and CYP3A4 activities and suppression of CYP2C9 activity in primary cultures of human hepatocytes. Additionally, clinical studies have been conducted to examine the potential for interactions with methylphenidate, dexamphetamine, warfarin, ethinylestradiol and triazolam (Robertson & Hellriegel, 2003). The only substantive interactions observed were with ethinylestradiol and triazolam, apparently through induction of CYP3A4, primarily in the gastrointestinal system. Overall, the results of interaction studies suggest that modafinil has potential to affect the pharmacokinetics of drugs that are metabolised by certain CYP enzymes. Compounds that induce or inhibit CYP activity are unlikely to have major effects on the pharmacokinetics of modafinil (Robertson & Hellriegel, 2003).

5.1.3.3. Modafinil: safety

The safety of Modafinil has been demonstrated in healthy volunteers (Wong *et al.*, 1999), patients with excessive daytime sleepiness (Boivin, Montplaisir, Petit, Lambert & Lubin, 1993; Besset, Chetrit, Carlander & Billiard, 1996; Broughton, Fleming, George, Hill, Kryger, Moldofsky, Montplaisir, Morehouse, Moscovitch & Murphy, 1997) and cocaine dependent patients (Malcolm, Book, Moak, DeVane & Czepowicz, 2002; Dackis, Lynch, Yu, Samaha, Kampman, Cornish, Rowan, Poole, White & O'Brien, 2003; Dackis, Kampman, Lynch, Pettinati & O'Brien, 2005). Moreover, a number of studies have provided evidence for its low potential for dependence (Jasinski & Kovacevic-Ristanovic, 2000; Menza, Kaufman & Castellanos, 2000; Rush, Kelly, Hays, Baker & Wooten, 2002; Myrick, Malcolm, Taylor & LaRowe, 2004).

5.1.3.4. Modafinil: efficacy

Animal models have shown modafinil to have similar wake promoting properties as amphetamine without subsequent rebound hypersomnolence (Edgar & Seidel,

1997). In humans, modafinil selectively improved neuropsychological task performance in healthy volunteers (Turner, Robbins, Clark, Aron, Dowson & Sahakian, 2003) and adult patients with attention deficit hyperactivity disorder (Turner, Clark, Dowson, Robbins & Sahakian, 2004). The finding that modafinil significantly reduced impulsive responding in these two studies has important implications for its potential in promoting abstinence by reducing impulsive amphetamine use. In studies among cocaine users, measures of impulsivity at baseline have been found to predict cocaine use and treatment retention (Moeller, Dougherty, Barratt, Schmitz, Swann & Grabowski, 2001).

While modafinil has a well established place as an effective treatment of the excessive daytime sleepiness associated with narcolepsy (Boivin *et al.*, 1993; Besset *et al.*, 1996; Broughton *et al.*, 1997) there has been recent interest in the use of modafinil in stimulant users. Dackis and colleagues have conducted preliminary investigations of the safety of modafinil use in cocaine users (Dackis *et al.*, 2003; Malcolm, Donovan, DeVane, Cochran, Hedden, Mojsiak, Elkashef, Kampman & Brady, 2004). These studies found that the co-administration of modafinil and a single dose of intravenous cocaine were not associated with medical risk in terms of blood pressure, pulse, temperature, or electrocardiogram measures. Pre-treatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving. In fact, cocaine euphoria was significantly blunted in one subjective measure (Dackis *et al.*, 2003). Further evidence for the efficacy of modafinil in the treatment of cocaine dependence was derived from a randomized, double-blind, controlled, eight week trial of modafinil (400mg per day) which found that modafinil-treated patients provided significantly more benzoylecgonine-negative urine samples over the eight week trial and were retained significantly longer in treatment in comparison to placebo group subjects (Dackis *et al.*, 2005).

There is only one published study of the use of modafinil in amphetamine dependence. This was a case study that showed modafinil to be effective in a patient with comorbid social phobia and amphetamine dependence (Camacho & Stein, 2002).

5.1.4. Summary

Based on the nature, time course and severity of amphetamine withdrawal symptoms identified in previous work, two drugs with the potential to be effective in amphetamine withdrawal were identified – the noradrenergic and serotonergic antidepressant, mirtazapine and wake-promoting drug, modafinil. Symptoms experienced during amphetamine withdrawal are thought to result from a relative depletion in the concentration of three neurotransmitters, dopamine, serotonin and noradrenaline. The selection of trial medications was based on their potential ability to alleviate withdrawal symptoms and restore concentrations of these neurotransmitters in the brain.

Mirtazapine is a safe, well-tolerated and effective medication for the treatment of depressive symptoms – a major feature of amphetamine withdrawal. However, while the efficacy and rapid onset of action in depression are desirable properties, the principal justification for its use in amphetamine withdrawal is the action of mirtazapine on catecholamine concentrations. That is, in blocking the reuptake of noradrenaline and to a lesser extent serotonin, mirtazapine may reverse the presumed depletion of these neurotransmitters, thus alleviating some of the aversive symptoms experienced during amphetamine withdrawal. The second pilot study drug, modafinil is safe, effective, well tolerated with low dependence potential, and has shown early promise in the treatment of psychostimulant dependence. Specifically, modafinil may be effective in alleviating the excessive sleepiness seen in the first week of amphetamine withdrawal (McGregor *et al.*, 2003, 2003, 2005). Because the safety and tolerability of these medications have not been tested in amphetamine withdrawal, an open label pilot trial was planned to assess these factors. Additionally, open-label trials are a useful method of choosing among a range of potential helpful medications for stimulant dependence (Kampman, Rukstalis, Ehrman, McGinnis, Gariti, Volpicelli, Pettinati & O'Brien, 1999).

This trial has the potential to provide evidence for the first safe and effective pharmacotherapy for amphetamine withdrawal and dependence. The identification of an effective pharmacological treatment would increase the range of treatment options currently available to amphetamine users seeking treatment for

amphetamine dependence. This outcome would have a two-fold effect in both attracting and retaining patients in treatment and in providing clinicians with an evidence-based pharmacological intervention for their amphetamine-dependent patients.

5.1.5. Aims

The principal aim of this trial was to evaluate the safety of two medications – mirtazapine and modafinil in dependent users undergoing inpatient amphetamine withdrawal treatment. Secondary aims were to assess the efficacy of these medications in ameliorating symptoms of amphetamine withdrawal and in treatment retention.

5.2. Method

Consecutive clients presenting for inpatient treatment of amphetamine dependence were assessed for consistency with the study criteria.

5.2.1. Study Design

Successive, open-label pilot pharmacotherapy studies compared to a single historical comparison group receiving treatment as usual.

5.2.2. Study setting

As for the Australian withdrawal study (see **Chapter 2**) and the ACSA development and evaluation study (see **Chapter 4**) data collection took place at Warinilla Clinic, a publicly funded substance use facility administered by Drug and Alcohol Services South Australia (DASSA) and located in metropolitan Adelaide, South Australia. DASSA is funded by the South Australian State Government and treatment is provided free of charge to all clients.

5.2.3. Ethical considerations

Ethics approval for the open label trials of modafinil and mirtazapine was received from the Royal Adelaide Hospital, Adelaide, South Australia.

5.2.4. Sample size

There is little guidance in the literature in determining an appropriate sample size for a pilot study. A review of the literature revealed a wide range of sample sizes in pilot trials of medications for new indications. Given the major aim of testing the safety and tolerability of the two novel medications for amphetamine withdrawal treatment, it was considered that a sample size of 12 in each group would be adequate to test the major aim.

5.2.5. Study subjects

A total of 49 subjects were enrolled in the three groups: 22 in the comparison group, 13 in the mirtazapine group and 14 in the modafinil group. The comparison group was drawn from the sample enrolled to test the validity of the ACSA (see **Chapter 4**). Only those subjects who had been enrolled in the ACSA study prior to the commencement of the pharmacotherapies study were included in the comparison group. **Table 5.1** shows the sample sizes for each group by day of abstinence.

Table 5.1 Group sample size by day of abstinence

	Day of abstinence										
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
TAU	6	8	7	11	8	5	3	3	2	2	2
Mirtazapine	5	9	13	13	10	10	7	6	6	5	4
Modafinil	7	11	14	14	12	10	9	9	8	7	6

Although some subjects in the comparison group left the clinic prior to completing treatment, there were no drop-outs from the study. Thirteen clients were enrolled in the mirtazapine trial. Of these, 12 subjects completed the minimum study requirements of at least four days of the study protocol (i.e., baseline data plus at least three days of study medication treatment and three days of questionnaire

completion subsequent to study medication treatment). The total data collection period was August 2003 – November 2004. Comparison group data (*n*=22) were collected between August 2003 and January 2004. Data collection for the mirtazapine pilot study (*n*=13) took place between January and May 2004 and for the modafinil pilot study (*n*=14) between May and November 2004.

Two subjects left the mirtazapine study because the medication was not 'working' and they did not like the feeling of lethargy/tiredness that they associated with the treatment. Of these two study drop-outs, one had completed the minimum four days of participation while the other subject withdrew consent to participate after two days of data collection and one day of study drug treatment. This latter subject was therefore replaced to facilitate the sample size target of 12 subjects.

Fourteen clients were enrolled in the modafinil trial. Of these, 12 subjects completed the minimum study requirements of at least four days of the study protocol (i.e., baseline data plus at least three days of study medication treatment and three days of questionnaire completion subsequent to study medication treatment). One subject found the medication ineffective and dropped out of the study after completing the minimum study requirements. A second subject left the clinic after two days stating that he 'felt well enough to go home'. A third subject left the clinic after three days following a conflict with another client. These latter two subjects were replaced to facilitate the sample size target of 12 subjects. Data from study drop-outs were included in the analysis.

5.2.6. Study criteria

Study criteria were similar to previous studies with additional exclusion criteria relating to the medications to be trialled (mirtazapine and modafinil).

5.2.6.1. Inclusion criteria

5.2.6.1.1. Aged 18 – 65 years

5.2.6.1.2. Urine positive for sympathomimetic amines

5.2.6.1.3. Used amphetamines for at least three days a week over the previous month

5.2.6.1.4. Used amphetamine within the previous 96 hours

5.2.6.1.5. Fulfils the DSM-IV criteria for amphetamine dependence (DSM-IV-TR, 2000)

5.2.6.1.6. Willing and able to provide informed consent to participate in the study

5.2.6.1.7. Considered likely to comply with study protocol

5.2.6.2. Core exclusion criteria

Below is a list of the exclusion criteria that are common to both mirtazapine and modafinil trials.

5.2.6.2.1. Known hypersensitivity to the study medication (either modafinil or mirtazapine depending on which medication is being tested at that time)

5.2.6.2.2. Pregnancy or lactation

5.2.6.2.3. Concurrent acute medical or psychiatric illness requiring acute care hospitalisation

5.2.6.2.4. Requirement for pharmacological treatment regime for other psychoactive substance withdrawal[4]

5.2.6.2.5. Current participant, or within three months of completing another drugs of dependence trial

5.2.6.2.6. Currently on methadone or buprenorphine maintenance

5.2.6.2.7. Use of monoamine oxidase inhibitors within the past fourteen days

[4] Pharmacological treatment regimes include: diazepam loading for alcohol withdrawal, diazepam regime for alcohol seizure prophylaxis and/or a benzodiazepine reduction regime. For opiate withdrawal: a buprenorphine reduction regime and/or clonidine withdrawal regime.

5.2.6.2.8. Planning to commence monoamine oxidase inhibitors within the next fourteen days

5.2.6.2.9. Currently taking any antidepressant medication

5.2.6.2.10. History of bipolar disorder

5.2.6.2.11. History of epilepsy

5.2.6.2.12. Hypertension unrelated to amphetamine use

5.2.6.2.13. History of glaucoma

5.2.6.2.14. Jaundice

5.2.6.2.15. Documented history of serious cardiac disease

5.2.6.2.16. Hypotension (Systolic pressure $<$ 90mmHg)

5.2.6.2.17. Diabetes mellitus

5.2.6.2.18. Unwilling or unable to participate in the study

5.2.6.2.19. Creatinine clearance < 30mL/min

5.2.6.2.20. ALT > 3 x upper limit of normal

5.2.6.2.21. Bilirubin > 40

5.2.6.3. Additional exclusion criteria: modafinil study

Because of the possibility of drug interactions, patients currently taking any of the following medications were excluded from the modafinil study: carbamazepine, cyclosporin, itraconazole, propanolol, ketoconazole, methylphenidate, phenobarbitone, phenytoin, rifampicin, theophylline, triazolam, tricyclic antidepressants or warfarin.

5.2.6.4. Additional exclusion criteria: mirtazapine study

5.2.6.4.1. Antidepressant induced hypomania

Because of the possibility of drug interactions, patients currently taking any of the following medications were excluded from the mirtazapine study: azole antifungals, carbamazepine, cimetidine, erythromycin, HIV protease inhibitors, nefazodone, phenytoin, rifampicin or St Johns Wort.

5.2.6.5. Criteria for withdrawal from study

The criteria for withdrawal from the study and hence cessation of treatment medication and resumption of treatment as usual were:

5.2.6.5.1. Withdrawal of consent for study participation

5.2.6.5.2. Serious or ongoing adverse reaction to the study medication

5.2.6.5.3. Development of condition requiring treatment with antipsychotic medication (e.g., paranoia or psychosis)

5.2.6.5.4. Development of any of the exclusion criteria during the study period

In addition, those patients discharged from the inpatient unit for breach of clinic rules ceased participation in the study. Data collected up until the occurrence of any withdrawal criterion were included in the analysis.

5.2.7. Study Instruments

For consistency with previous studies (see **Chapters 2** and **3**), the same instruments and methodology (with some exceptions) were used for the pilot pharmacotherapies study. For the present study, the data collection period was eleven days and an additional two questionnaires were used.

5.2.7.1. Screening instruments

5.2.7.1.1. Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1997) (Module for amphetamine dependence)

5.2.7.2. Instruments administered on admission to study

5.2.7.2.1. Structured interview schedule assessing demographic data and drug use history

5.2.7.2.2. Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1997) (Module for major depressive disorder)

5.2.7.2.3. Beck Depression Inventory II (BDI) (Beck *et al.*, 1996)

5.2.7.2.4. The Severity of Dependence Scale (SDS) (Gossop *et al.*, 1995)

5.2.7.3. Instruments administered daily

5.2.7.3.1. Amphetamine Withdrawal Questionnaire (AWQ) (Srisurapanont *et al.*, 1999)

5.2.7.3.2. Amphetamine Cessation Symptom Assessment (ACSA) (McGregor *et al.*, 2004)

5.2.7.3.3. St Mary's Hospital Sleep Questionnaire (SMHSQ) (Ellis *et al.*, 1981)

5.2.7.3.4. Clinical Global Impressions scale (CGI) (Guy, 1976)

See Section 2.2.8 above, for a full description of the above study instruments.

5.2.7.3.5. General Well-being scale

A single item scale measured general well-being (see **Item 5.2.7.3.5 above**) on a scale of 0 – 8 with higher scores indicating greater well-being.

5.2.7.3.6. Drug Effects Questionnaire (Rush *et al.*, 2002)

A drug effects questionnaire (see **Item 5.2.7.3.6 above**) used in an evaluation of modafinil in cocaine users was adapted for use in the present study (Rush *et al.*, 2002). This eight item scale measured domains of drug 'liking', 'high', willingness

to take the drug again, willingness to pay for the drug, increased energy, stimulation, amphetamine craving and 'rush' on a scale of 0 – 4 with higher scores indicating greater intensity of effect.

5.2.8. Data collection and collation

At the time of data collection, the usual length of stay in the inpatient unit for medical treatment of amphetamine withdrawal was 7 – 10 days. Questionnaires were completed once daily and data collated according to the (self-reported) time since last use. That is, data collected within 24 hours of the last use of amphetamines were designated 'Day 0'; data collected 24 – 48 hours following the last use of amphetamines were designated 'Day 1' etc. Thus, the maximum number of data collection days for individual subjects was eleven (days 0 – 10).

It is important to note that subjects may have been at different time points in the withdrawal process when entering the clinic (and therefore the study) for treatment. Additionally, for some study subjects treatment extended beyond the time frame of the study as data were only collected for the first eleven days (days 0 – 10) following the last use of amphetamines. However, beyond the tenth day of abstinence, subject numbers were too low for statistical analysis.

5.2.9. Data analyses

Variations over time were measured using a Linear Mixed Model ANOVA with day of abstinence and group allocation as fixed factors. Post-hoc Bonferroni tests were used to identify significant group or time point differences. Differences between groups on normally distributed continuous variables were determined using Student's *t*–test for independent groups. Homogeneity of variance is one of the assumptions of the Student's *t*-test. This assumption was tested by Levene's test, run in conjunction with the Student's *t*-test. SPSS produces two results when a *t*-test is used. One, which assumes homogeneity of variance and a second, which does not. Where Levene's test for equality of variance was significant, indicating that the assumption of homogeneity of variance had been violated, the result of the more conservative *t*-test result has been reported. Where continuous variables were highly skewed, medians were reported. Pearson's product-moment correlation coefficient was reported for normally distributed continuous variables.

The level for the acceptance of significance (Alpha) was set at 0.05. Significance levels > 0.05 and ≤ 0.10 were considered as trends toward significance. Confidence intervals of 95% were used. Analyses were conducted using SPSS V11.5 for Windows.

5.2.10. Procedure

5.2.10.1. Study admission

Consecutive inpatient admissions to Warinilla Clinic (Drug and Alcohol Services South Australia) were screened for their suitability as study subjects. Twelve subjects were required for each trial. Recruitment continued until 12 subjects each completed at least three days of study drug treatment and data collection (i.e., administration of study instruments). Potential subjects undertook a two-phase process prior to study enrolment.

5.2.10.2. Pre-admission screening: Phase 1

Potential study subjects (i.e. those inpatients who had been identified as meeting the basic study criteria) were given a verbal explanation of the aims of the study and the implications of their participation. Interested patients were provided with written information in the form of the study information sheet and consent form to read (see **Appendix 5**). Patients were given adequate time to read these documents, to ask questions and to discuss their participation in the study with others. Interested clients were given a full and detailed explanation of the implications of their participation in the study. Once any concerns were discussed and satisfactorily resolved, informed consent was obtained.

5.2.10.3. Pre-admission screening: Phase 2

Once informed consent had been obtained, patients were screened for consistency with the remaining study criteria. For those subjects who met all inclusion criteria and none of the exclusion criteria, an extensive drug use and treatment history was taken. Potential subjects then underwent a complete medical assessment including medical and psychiatric history. Subjects who did

not meet the study criteria received the standard clinic treatment for amphetamine withdrawal.

5.2.10.4. Administration of study medication

The aim of the study medication protocol was to achieve the maximum therapeutic dose of each study drug as rapidly as possible while minimising the possibility of side effects. As the study was designed to identify safe, well tolerated and potentially effective pharmacotherapies for acute amphetamine withdrawal symptoms, study drug administration was limited to the acute withdrawal period of 10 days (based on the findings from the earlier withdrawal studies). This study design meant that subjects received the study medication for varying periods of time within the acute withdrawal period.

For example, it is common for patients to attempt to reduce amphetamine use prior to admission for inpatient treatment. At the time of admission, it may be several days since they had last used amphetamines. Therefore study subjects received the study drug for varying periods. Those admitted soon after taking their last dose of amphetamines received the study drug for a greater number of days in comparison to subjects admitted several days after their last use. As the study medication was only administered for the first ten days of abstinence, only patients who had used amphetamines within the previous 96 hours were recruited into the study.

5.2.10.5. Initiation of study drug treatment

Administration of each study drug commenced only when informed consent was obtained, study screening and admission documentation completed and the subject's aggregate score on the Amphetamine Withdrawal Questionnaire (AWQ) was ≥ 10. Following the initial dose and dose increments, subjects were monitored regularly by nursing staff. Monitoring included observation of and questioning about symptoms and signs of discomfort. Additionally, as patients were typically ambulant during inpatient treatment, they were encouraged to report any adverse effects of the study drug or other symptoms to clinic staff. Effects (including side-effects) of the study medication were formally assessed on a daily basis by a

member of the research team. Vital signs were measured and recorded twice daily.

Symptomatic medication and/or nursing care measures (e.g., observation, assessment, explanation and reassurance, bed rest, encouragement of fluid intake) were used to manage mild side effects of the study drug where they occurred.

5.2.10.6. Duration of study drug treatment

In each trial, study medication was administered for a maximum of ten days calculated from the subject's self-reported day of last amphetamine use. Therefore within the maximum of ten days, the duration of study medication treatment was determined by two factors:

5.2.10.6.1. Time between the last use of amphetamines and admission to the study

5.2.10.6.2. Amphetamine withdrawal symptoms – aggregate score on the AWQ must be $\geq$ 10 before study medication commenced[5]

5.2.10.7. Completion of study drug treatment

To minimise the possibility of adverse effects from discontinuation of the study drug, for both study medications, doses were reduced by half on the final day of study medication treatment. Additionally, subjects were monitored for at least 24 hours following the last dose of study medication to assess any adverse effects of discontinuation. Following this final 24 hour monitoring period, subjects were discharged from the clinic providing they were medically fit to leave and aftercare (where desired by the patient) had been arranged.

[5] In practice, there were no cases in which medication treatment was delayed because of low AWQ scores

5.2.10.8. Duration of inpatient stay

Therefore, for the purposes of the study, the maximum duration of stay in the inpatient clinic was 11 days. The standard length of inpatient treatment for amphetamine withdrawal in Warinilla is 7 – 10 days but can vary with the severity of withdrawal symptoms experienced by individual patients. Additionally, some patients may require a longer stay to facilitate transfer to a rehabilitation facility or for other non-medical reasons.

5.2.10.9. Modafinil: dosage and administration

Daily doses of modafinil 400mg were administered orally in divided doses of 200mg morning and noon. This dosage level is within the recommended guidelines and had been well tolerated by patients in previous studies including those with cocaine dependent patients (Dackis *et al.*, 2003; Dackis *et al.*, 2005). **Table 5.2** details the dosing protocol for the modafinil study.

Table 5.2 Study drug administration protocol: modafinil

Day of modafinil treatment	1	2	3	4	5	6	7	8	9	10	
Modafinil dose (mg)	400	400	400	400	400	400	400	400	400	200	0
Day of abstinence	0	1	2	3	4	5	6	7	8	9	10

While the manufacturer's recommendations do not indicate the need to gradually increase initial doses of modafinil, or to decrease doses gradually on cessation of treatment, a half dose was administered on the final day of modafinil treatment to minimise any possibility of discontinuation effects. For example, subjects admitted within 24 hours of having self-administered amphetamine (day 0) and who stayed in the study for 11 days (days 0 – 10), received the full 400mg dose of modafinil treatment for nine days plus one day at half dose. Subjects admitted to the study on the first day of abstinence received a maximum of eight days of modafinil at the full dose plus one day at half dose. Those admitted on the second day of abstinence received a maximum of seven days of modafinil at the full dose plus

one day at half dose. Subjects admitted on the third day of abstinence received a maximum of six days of modafinil at the full dose plus one day at half dose while subjects admitted on the fourth day of abstinence received a maximum of five days of modafinil treatment at the full dose plus one day at half dose.

5.2.10.10. Mirtazapine: dosage and administration

To minimise the possibility of adverse effects, mirtazapine therapy (administered orally) was initiated by means of incremental increases in dosage over a three-day period. As detailed in **Table 5.3**, mirtazapine dosage commenced at 15 mgs nocte on the first day, 30 mg nocte the second day, then 60 mg nocte on the third day. Subjects remained on 60 mg until the eighth day of abstinence. To minimise the possibility of discontinuation effects, a half dose was administered on the final day (day nine of abstinence) of study drug treatment.

For example, subjects admitted within 24 hours of self-administered amphetamine (day 0) received the full 60mg dose of mirtazapine for seven days, providing they stayed in the study for the full 11 days. Subjects admitted to the study on the first day of abstinence received a maximum of six days of mirtazapine at the full dose. Those admitted on the second day of abstinence received a maximum of five days of mirtazapine at the full dose.

Table 5.3 Study drug administration protocol: mirtazapine

Day of mirtazapine treatment	1	2	3	4	5	6	7	8	9	10	
Mirtazapine (mg)	15	30	60	60	60	60	60	60	60	30	0
Day of abstinence	0	1	2	3	4	5	6	7	8	9	10

Subjects admitted on the third day of abstinence received a maximum of four days of mirtazapine at the full dose while subjects admitted on the fourth day of abstinence received a maximum of three days of mirtazapine at the full dose. These dosages are within the manufacturer's recommendations for mirtazapine administration.

5.2.10.11. Symptomatic medication for amphetamine withdrawal

All study medication treatment took place under 24 hour medical care in the inpatient section of Warinilla Clinic (see **Table 5.4**). Symptomatic medication was available on an as needed basis to all study subjects.

Table 5.4 Symptomatic medication protocol for amphetamine withdrawal symptoms

Medication	Indication	Dosage	Route	Frequency
Diazepam	Anxiety/agitation	5 – 10mg	Oral	qid prn
Either Nitrazepam	Insomnia	5 – 10mg	Oral	nocte prn
or Temazepam	Insomnia	10 – 20mg	Oral	nocte prn
Paracetamol	Analgesia	500 – 1000mg	Oral	4/24 prn
Naproxen	Analgesia	250mg	Oral	tds prn

5.2.11. Outcome measures

The principal outcome measure was the safety and tolerability of mirtazapine and modafinil as assessed by:

5.2.11.1.1. Side effects of study medication treatment

Secondary outcome measures included:

5.2.11.1.2. Self-reported and observer-rated amphetamine withdrawal severity

5.2.11.1.3. Self-reported general well-being

5.2.11.1.4. Self-reported sleep patterns

5.2.11.1.5. Amount and type (benzodiazepines and analgesics) of symptomatic medication administered

5.2.11.1.6. Retention in treatment

5.2.11.2. Historical comparison group

Amphetamine withdrawal severity, amount and type of concurrent symptomatic medication administered and retention in treatment were compared to an historical comparison group from a previous study of inpatient amphetamine withdrawal conducted at the same clinic. The comparison group comprised the first 22 subjects from the psychometric testing of the ACSA study (see **Chapter 4**). Only those subjects who had been enrolled in the ACSA study prior to the commencement of the pilot trials were included in the comparison group.

5.3. Results Section 1: Comparison of the three study groups

5.3.1. Sample characteristics

Characteristics of the sample are shown in **Table 5.5**.

Table 5.5 Characteristics of the study sample

Characteristics	**Comparison (*n* = 22)**	**Mirtazapine (*n* = 13)**	**Modafinil (*n* = 14)**
Age; mean years (range)	31 (19 – 45)	32 (23 – 42)	31 (24 – 36)
Male *n* (%)	11 (50)	7 (54)	9 (64)
Unemployed *n* (%)	14 (64)	13 (100)	11 (79)
Married/cohabiting *n* (%)	5 (23)	2 (15)	3 (21)
Education (years) mean (range)	10 (7 – 12)	10 (7 – 12)	11 (8 – 14)
Age first used amphetamine; median years (range)	19 (15 – 38)	21 (13 – 33)	18 (16 – 34)
Age first regular amphetamine use; median years (range)	23 (15 – 38)	22 (16 – 33)	21 (16 – 34)
Length of amphetamine use; mean years (range)	9 (1 – 25)	11 (3 – 19)	10.2 (2 – 18)
Length of regular amphetamine use; mean years (range)	7 (<1 – 17)	9 (3 – 17)	7 (<1 – 18)
Severity of Dependence Scale; mean (range)	9.6 (3 – 14)	12 (9 – 15)	11 (5 – 15)

There were no significant differences between the three study groups in terms of the baseline demographic or substance use variables measured for this study. Characteristics of the three study groups were comparable to those found for the first Australian withdrawal study (see **Chapter 2**). Most subjects were single, unemployed and in their early 30s at the time of treatment entry. As for the first Australian study, all subjects were long-term, severely dependent amphetamine users.

5.3.2. Measures of recent amphetamine use

Similarly, there were no differences between the three groups on amphetamine and other drug use during the month prior to treatment entry (**see Table 5.6**).

Table 5.6 Measures of recent amphetamine use patterns

Measures of amphetamine use in the previous month	**Comparison (*n* = 22)**	**Mirtazapine (*n* = 13)**	**Modafinil (*n* = 14)**
Days of amphetamine use; mean (range)	24 (14 – 30)	22 (14 – 30)	25 (15 – 30)
Grams per day; median (range)	1.0 (0.3 – 6.5)	0.75 (0.1 – 4.5)	0.75 (0.1 – 6)
Frequency per day used; median (range)	3 (1 – 10)	2 (1 – 9)	2 (1 – 6)
Cost per day (AUD$); median (range)	171 (50 – 500)	198 (50 – 500)	163 (50 – 850)
Substance types used; mean (range)	3.8 (1 – 9)	3.9 (2 – 7)	4.0 (3 – 6)

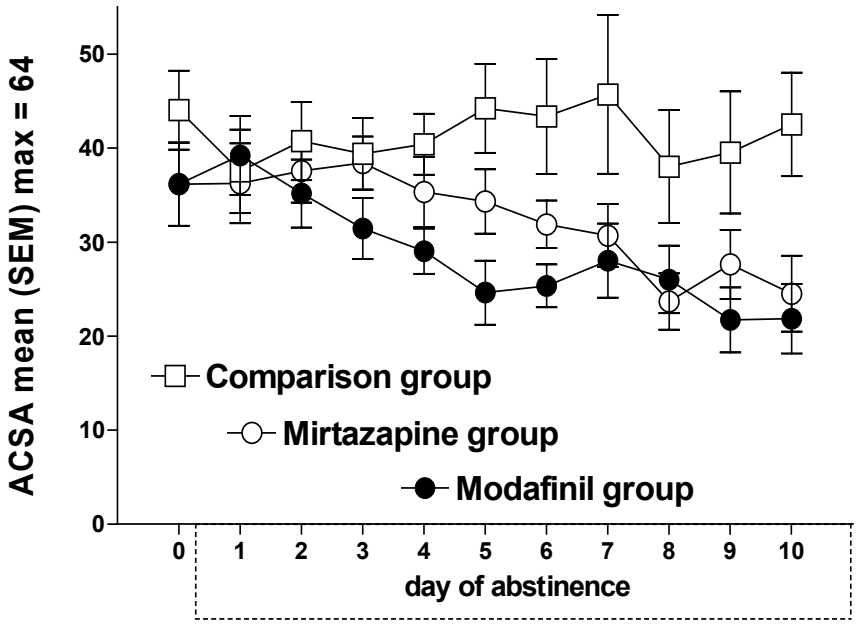
Although dependence (according to DSM-IV Criteria) on substances other than amphetamines (with the exception of nicotine) was an exclusion criterion, polydrug use was common. Principle other substances used were tobacco, cannabis, alcohol and benzodiazepines.

5.3.3. Time course and severity of withdrawal symptoms

There were no significant differences between the three groups on ACSA scores on day 0 of abstinence (p = 0.90) or on the day of admission (p = 0.28). Using the aggregate ACSA score as the dependent variable, group differences in the time course and severity of amphetamine withdrawal symptoms were analysed using a linear mixed model with day of abstinence and study group as fixed factors (see **Figure 5.1**).

Overall, there were significant differences between the groups in the severity of withdrawal symptoms over days 0 – 10 of abstinence (F = 18.6, df 2,219 p< 0.001). Post-hoc Bonferroni tests showed that aggregate ACSA scores were significantly higher in the comparison group (mean = 40.9, SEM = 1.3) compared to both the modafinil group (mean = 33.7, SEM = 1.1, p = 0.001) and the mirtazapine group (mean = 33.7, SEM = 1.1, p = 0.001). Additionally, aggregate ACSA scores were significantly lower in the modafinil group compared to those for mirtazapine group subjects (p = 0.041).

Figure 5.1 Time course and severity of withdrawal symptoms



The time course of aggregate ACSA scores was investigated separately for the three study groups. There was no significant change in withdrawal severity as

measured by ACSA scores for either the comparison (p = 0.66) or the mirtazapine group subjects (p = 0.09) although there was a trend in the direction of significance for the latter group. Only modafinil treated subjects showed significant change in withdrawal severity over the study period (F = 3.6, df 10,84 p < 0.001). By the end of the first week of abstinence, withdrawal severity was similar in both mirtazapine and modafinil treated subjects while scores remained elevated in the comparison group.

5.3.4. Distribution of ACSA factor scores

Factor analysis of the ACSA (see **Chapter 4**) identified three distinct symptom clusters that characterised amphetamine withdrawal and could function as subscales; 'Anxiety and Craving', 'Hypersomnia' and 'Depression' (see **Figure 5.2**).

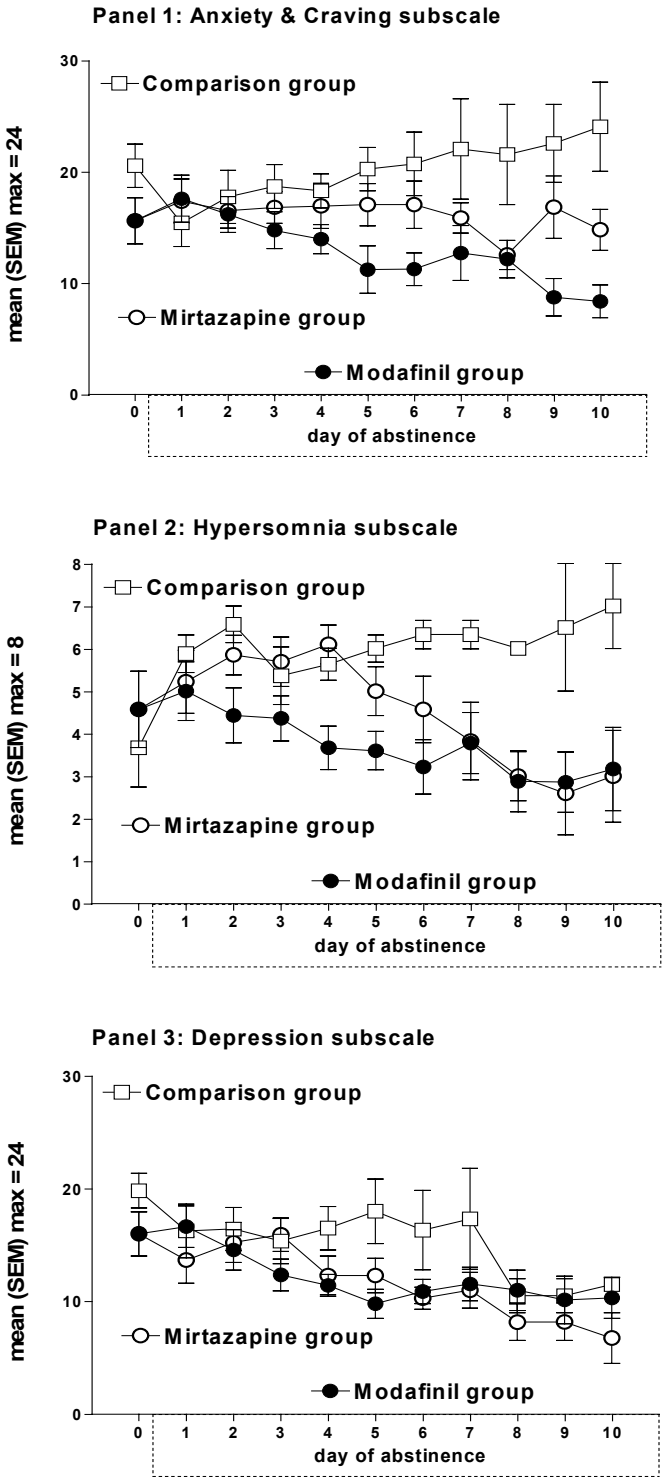
Differences between the three study groups in terms of the ACSA subscales were analysed using a linear mixed model with day of abstinence and study group as fixed factors.

5.3.5. Distribution of the first subscale 'Anxiety and Craving'

Distributions of the first subscale 'Anxiety and Craving' are shown in **Figure 5.2: Panel 1**. There was a significant group effect (F = 24.1, df 2,219 p < 0.001). Post-hoc Bonferroni tests identified significant differences between aggregate 'Anxiety and Craving' subscale scores for the comparison group (mean = 19.0, SEM 0.7) and both the modafinil group (mean = 13.4, SEM = 0.6, p = 0.001) and the mirtazapine group (mean = 16.3, SEM = 0.6, p = 0.016). There was also a significant difference between modafinil and mirtazapine group subjects on this subscale (p = 0.002).

To identify temporal effects in 'Anxiety and Craving' subscale scores, changes over time were investigated separately for the three study groups. There was no significant change in withdrawal severity as measured by the 'Anxiety and Craving' subscale for the comparison (p = 0.42) and mirtazapine group subjects (p = 0.88). Only modafinil treated subjects showed significant change in 'Anxiety and Craving' over the study period (F = 3.2, df 10,84 p < 0.001).

Figure 5.2 Distribution of ACSA subscales



5.3.6. Distribution of the second subscale 'Hypersomnia'

Differences in the second subscale 'Hypersomnia' are shown in **Figure 5.2: Panel 2**. There was a significant group effect (F = 18.2, df 2,219 $p < 0.001$). Post-hoc Bonferroni tests identified significant differences between aggregate 'Hypersomnia' subscale scores for the comparison group (mean = 5.7, SEM = 0.2) and both the modafinil group (mean = 3.9, SEM = 0.2, $p = 0.001$) and the mirtazapine group (mean = 4.9, SEM = 2.1, $p = 0.034$). There was also a significant difference between the modafinil group and mirtazapine group subjects ($p = 0.002$).

To identify temporal effects in 'Hypersomnia' subscale scores, changes over time were investigated separately for the three study groups. There was no significant change in withdrawal severity as measured by the 'Hypersomnia' subscale for the comparison ($p = 0.54$) or modafinil treated subjects ($p = 0.10$). Only mirtazapine group subjects showed significant change in 'Hypersomnia' over the study period (F = 2.9, df 10,66 $p < 0.004$).

5.3.7. Distribution of the third subscale 'Depression'

Differences in the third subscale 'Depression' are shown in **Figure 5.2: Panel 3**. There was a significant group effect (F = 6.7, df 2,219 $p < 0.001$). Post-hoc Bonferroni tests identified significant differences between aggregate 'Depression' subscale scores for the comparison group (mean = 16.1, SEM = 0.8) and both the modafinil group (mean = 12.4, SEM = 0.5, $p = 0.001$) and the mirtazapine group (mean = 12.6, SEM = 0.6, $p = 0.001$). There was no difference between the modafinil group and the mirtazapine group subjects ($p = 1.0$).

To identify temporal effects in 'Depression' subscale scores, changes over time were investigated separately for the three study groups. There was no significant change in withdrawal severity as measured by the 'Depression' subscale for the comparison group ($p = 0.18$). Both mirtazapine treated subjects (F = 3.2, df 10,65 $p < 0.002$) and modafinil treated subjects (F = 3.0, df 10,86 $p < 0.002$) showed significant change in 'Depression' over the study period.

Therefore, comparison group subjects had significantly greater severity of withdrawal symptoms compared to both the modafinil and the mirtazapine group on aggregate ACSA and the three subscale scores. Mirtazapine group subjects had significantly greater severity of withdrawal symptoms compared to subjects who received modafinil on the aggregate ACSA and two of three subscale scores. Only the intensity of the 'Depression' subscale score did not differ significantly between the mirtazapine and modafinil group subjects.

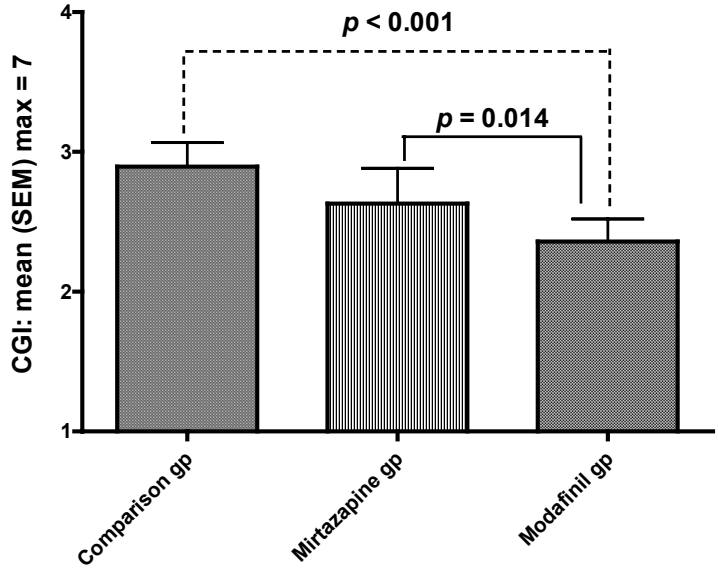
Only modafinil treated subjects showed a significant reduction in aggregate withdrawal scores, 'Anxiety and Craving' and 'Hypersomnia' subscale scores over the first 0 – 10 days of abstinence while both mirtazapine and modafinil treated subjects showed significant temporal change in the 'Depression' subscale score.

5.3.8. Observer-rated withdrawal severity

Observer-rated withdrawal severity (CGI scores) was measured on a range of 0 – 7, with higher scores indicating greater severity, for the three study groups (see **Figure 5.3**). Observer-rated withdrawal severity was significantly different between the three groups (F = 4.1, df 2,219, p = 0.016). Post-hoc Bonferroni tests identified a significant difference between CGI scores for comparison group subjects (mean = 3.1, SEM = 0.13) and modafinil group subjects (mean = 2.4, SEM = 0.11, p = 0.001). There was also a significant difference between modafinil and mirtazapine group subjects (mean = 2.9, SEM = 0.13, p = 0.014).

However, there were no significant differences between comparison and mirtazapine group subjects in terms of observer-rated withdrawal severity.

Figure 5.3 CGI scores for the three study groups

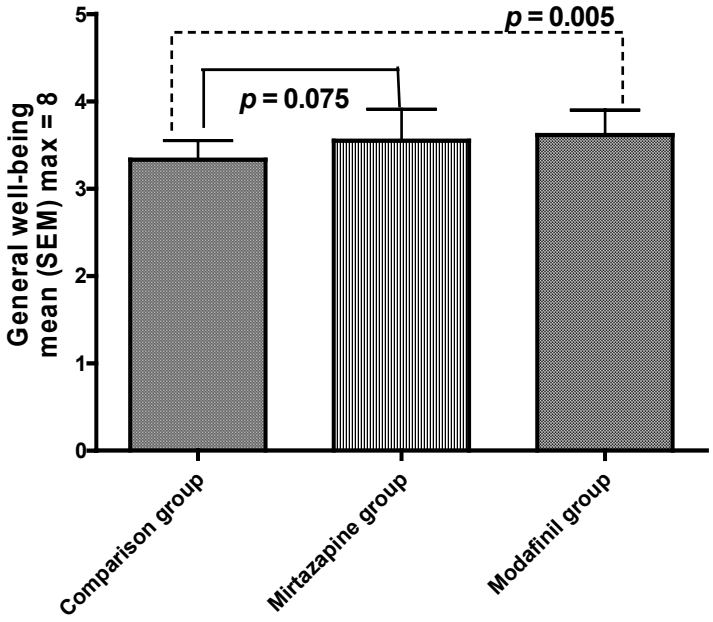


5.3.9. General well-being

Figure 5.4 shows the pattern of self-reported general well-being (measured on a scale of 0 – 8 with higher scores indicating greater well-being). There was a significant group effect (F = 7.8, df 2,219 p = 0.001) for this measure. Post-hoc Bonferroni tests identified a significant difference in general well-being between comparison group subjects (mean = 2.3, SEM = 0.29) and modafinil group subjects (mean = 3.5, SEM = 0.22; p = 0.005). There was a trend towards significance between the comparison group and the mirtazapine group (mean = 3.2, SEM = 0.22; p = 0.075).

However, there were no significant differences between mirtazapine and modafinil group subjects in terms of self-reported general well-being during amphetamine withdrawal.

Figure 5.4 General well-being



5.3.10. Vital signs

All vital signs remained within normal limits for the duration of the study. There were no significant differences between groups for temperature, radial pulse and respiration. However, there were significant differences in systolic (F = 4.3, df 2,213 p = 0.014) and diastolic blood pressure (F = 7.7, df 2,213 p = 0.001). Post Hoc Bonferroni tests showed that systolic blood pressure was significantly higher in modafinil treated subjects (mean = 127.61, SEM = 1.3) compared to those receiving treatment as usual (mean = 121.5, SEM = 2.1). Diastolic blood pressure in modafinil treated subjects (mean = 84.8, SEM = 0.9) was significantly higher than in mirtazapine treated subjects (mean = 79.7, SEM = 1.2) and subjects receiving treatment as usual (mean = 78.5, SEM = 1.6). Modafinil treated subjects had higher systolic and diastolic blood pressure on treatment entry but these differences remained even after controlling for admission blood pressure. However, while differences in blood pressure reached statistical significance, they were not clinically significant.

5.3.11. Administration of other medications

As for the previous withdrawal studies (see **Chapters 2** and **3**), all benzodiazepines administered (hypnotics and anxiolytics) were converted into diazepam equivalents (Ciraulo & Greenblatt, 1995) to provide a single continuous variable for analysis. There were no differences between study groups in the amount (mg) of benzodiazepines administered during the study period. On the days benzodiazepines were administered, the mean amount (mg equivalent of diazepam) administered per day was 25.05 (SEM = 0.82) mg. Similarly, there were no differences between study groups on the number of days on which analgesia was administered during the first 0 – 10 days of abstinence. On the days pericyazine was administered to comparison group subjects, the mean amount of pericyazine (mg) administered per day was 11.56 (SEM = 1.03) mg.

5.3.12. Retention in treatment

There were no statistically significant differences between study groups in terms of retention in treatment (see **Table 5.7**).

Table 5.7 Retention in treatment

Retention	**Comparison (*n* = 22)**	**Mirtazapine (*n* = 13)**	**Modafinil (*n* = 14)**
Treatment complete *n* (%)	11 (50)	7 (54)	8 (57)
Treatment incomplete *n* (%)	11 (50)	4 (31)	5 (36)
Study drop out *n* (%)	0	2 (15)	1 (7)
Days in treatment, mean (SEM)	6.6 (0.7)	8.1 (0.1)	8.6 (1.1)

Subjects who left the clinic prior to completing treatment did so for a variety of reasons including conflict with other clients, concern about partner or family matters or feeling well enough to leave. Two subjects left the mirtazapine study because the medication was not ‘working’ and they did not like the feeling of

lethargy/tiredness that they associated with the treatment. One subject left the modafinil study because the medication was 'ineffective'.

5.4. Results Section 2: Comparison of the mirtazapine and modafinil groups

The following section reports on the results of comparisons between the mirtazapine and the modafinil groups only.

5.4.1. Other symptoms reported during amphetamine withdrawal

Subjects receiving either mirtazapine or modafinil treatments were asked to indicate the incidence and severity of any symptoms not covered by the instruments used in the study. These symptoms were measured with the same response set as the ACSA i.e. on a range of 0 – 4, with higher numbers indicating greater severity.

The number of other symptoms reported was similar for both groups (p = 0.73) (see **Table 5.8**). All other symptoms were mild and transient, responding readily to symptomatic medications. For subjects receiving mirtazapine the most common other symptom was that of aches and pains while for those receiving modafinil, headache was the most frequently reported symptom. No serious adverse effects occurred during the study.

Table 5.8 Other symptoms reported during amphetamine withdrawal

	Mirtazapine		Modafinil	
Symptom	**n**	**%**	**n**	**%**
Aches and pains	6	46	1	7
Headache	3	23	5	36
Abdominal cramps	2	15	1	7
Diarrhoea	2	15	1	7
Dry mouth	2	15	1	7
Nausea	2	15	2	14
Mouth numbness	2	15	0	0
Breathlessness	1	8	0	0
Dizziness	1	8	0	0
Feel weird	1	8	0	0
Foggy head	1	8	0	0
Hangover	1	8	0	0
Leg cramps	1	8	0	0
Night sweats	1	8	0	0
Thirst	1	8	0	0
Toothache	1	8	0	0
Urinary frequency	1	8	0	0
Visual disturbances	1	8	0	0
Vomiting	1	8	0	0
Constipation	0	0	2	14
Electric shocks	0	0	1	7
Hot flush	0	0	1	7
Labile mood	0	0	1	7
Loss of appetite	0	0	2	14
Sweating	0	0	1	7
Tremor	0	0	2	14
Urinary retention	0	0	1	7

5.4.2. Depression

There were no differences between the modafinil and the mirtazapine groups on measures of depression on admission. Two measures of depression were used – the MINI module for major depressive episode (MDE) (see **Item 5.2.7.2.2 above**) and the BDI (see **Item 5.2.7.2.3 above**). **Table 5.9** shows the in-treatment (current) and historical pattern of major depressive episodes for both study groups.

Table 5.9 Major Depressive Episode

Major Depressive Episode (MDE)	**Mirtazapine (*n* = 12)***	**Modafinil (*n* = 14)**
Current MDE *n* (%)	12 (100)	11 (79)
Recurrent MDE *n* (%)	8 (67)	5 (39)
Past MDE *n* (%)	10 (83)	10 (77)

* one subject refused to complete the MINI

Almost all subjects were experiencing a current major depressive episode and many had a history of past and recurrent episodes.

There were no differences between mirtazapine and modafinil group subjects on admission BDI scores. **Table 5.10** shows the BDI depression severity groupings during the study period. On average, admission BDI scores fell into the severe category for both the mirtazapine (mean = 32.8, SEM = 2.8) and the modafinil (mean = 31.9, SEM = 3.0) group subjects. The majority of subjects in both groups fell into the moderate or severe depression category on admission for inpatient treatment.

Table 5.10 BDI depression severity groupings

Group	BDI severity groupings			
	0 – 13 Minimal	**14 – 19 Mild**	**20 – 28 Moderate**	**29 – 63 Severe**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Mirtazapine (*n* = 12)*	0	0	4 (33)	8 (67)
Modafinil (*n* = 14)	0	2 (14)	4 (29)	8 (57)

one subject refused to complete the BDI

5.4.3. Sleep patterns during amphetamine withdrawal

Differences in sleep patterns between the mirtazapine and the modafinil groups were analysed using a linear mixed model with day of abstinence and group as fixed factors (see **Figure 5.5**).

5.4.4. Total hours of sleep

Differences in the total hours of sleep (in one 24 hour period) are shown in **Figure 5.5: Panel 1**. There was a significant effect of time for the total hours of sleep (F = 2.6, df 10,173 p = 0.005). Group differences (F = 10.0, df 1,173 p = 0.002) were also identified, with the mirtazapine group (mean = 11.9, SEM = 0.6 hours) sleeping significantly longer in comparison to subjects treated with modafinil (mean = 9.0, SEM = 0.3) hours.

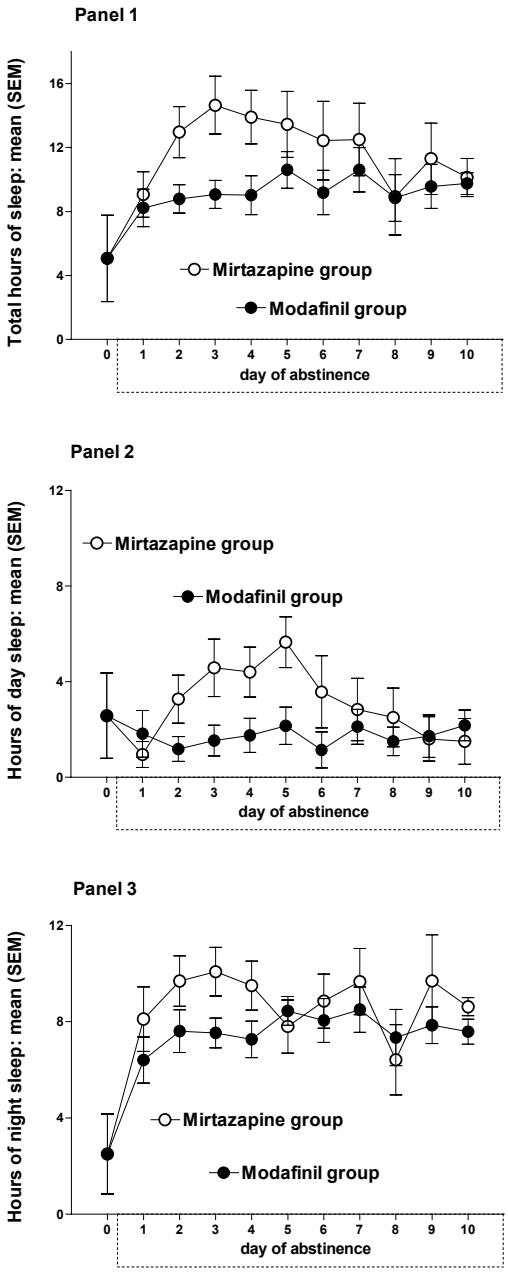
5.4.5. Day time sleep

For day time sleep, there was a significant group effect (F = 6.3, df 1,173 p = 0.012) see **Figure 5.5: Panel 2**. Subjects receiving mirtazapine treatment slept significantly longer during the day (mean = 3.2, SEM = 0.3 hours) in comparison to modafinil treated subjects (mean = 1.7, SEM = 0.2 hours).

5.4.6. Night time sleep

Analysis of hours of sleep during the night identified a significant effect of both time (F = 3.8, df 10,173 p = 0.001) and group (F = 6.0, df 1,173 p = 0.015), see **Figure 5.5: Panel 3**. Mirtazapine treated subjects reported significantly more hours of night time sleep (mean = 8.7, SEM = 0.3 hours) in comparison to modafinil treated subjects (mean = 7.2, SEM = 0.2 hours).

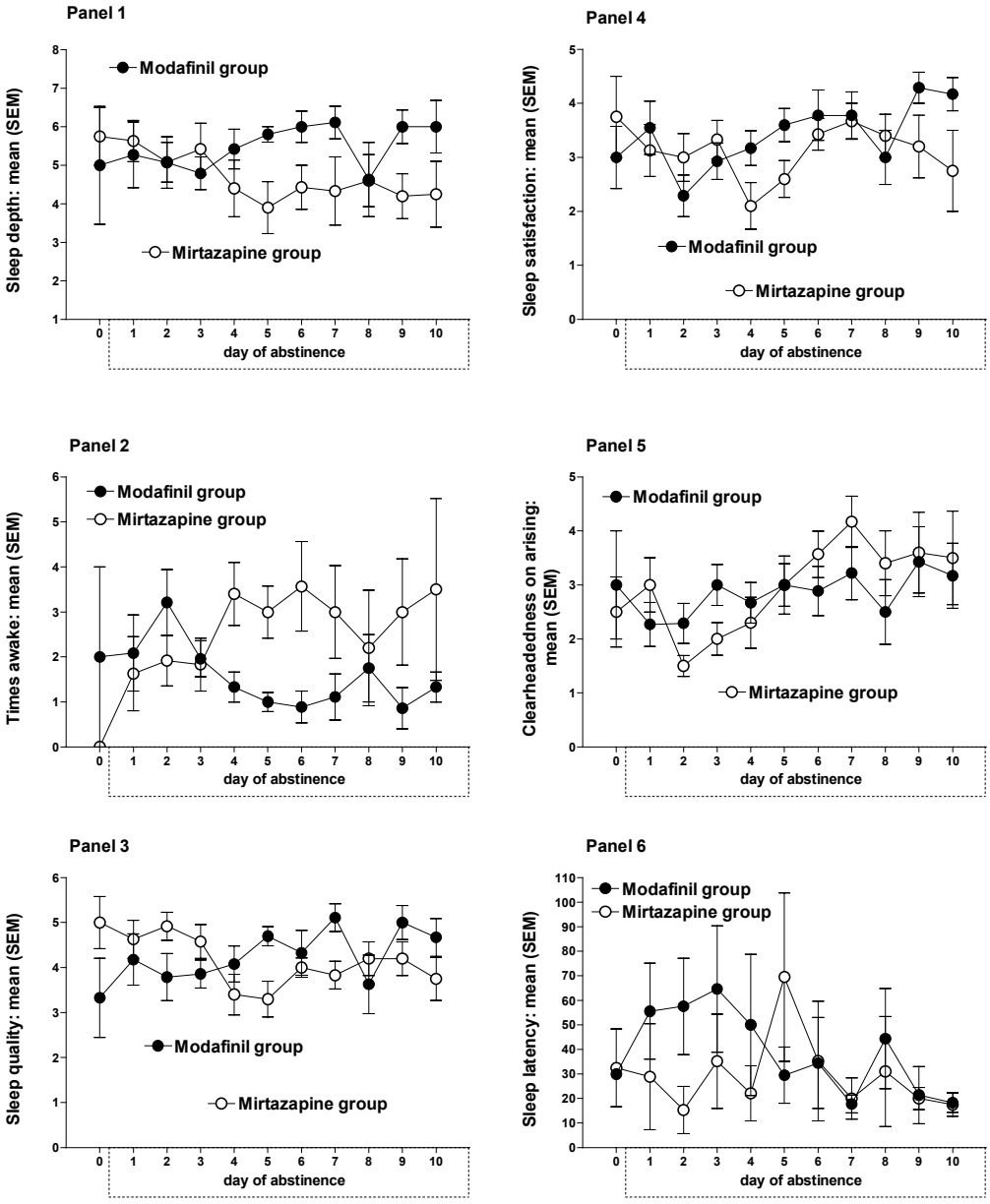
Figure 5.5 Sleep patterns



5.4.7. Sleep characteristics

Subjects who received modafinil had a greater depth of sleep (see **Figure 5.6: Panel 1**) in comparison to those who received mirtazapine (F = 5.6, df 1,164 p = 0.019).

Figure 5.6 Sleep characteristics



Mirtazapine treated subjects woke significantly more times (mean = 2.4, SEM = 0.2, F = 6.8, df 1,164 p = 0.010) in comparison to those who received modafinil (mean = 1.7, SEM = 0.1). There was also a significant interaction effect (F = 2.3, df

10,164 p = 0.014) for night time awakenings (**Figure 5.6: Panel 2**). While there were no differences between the mirtazapine and modafinil groups in terms of sleep quality (**Figure 5.6: Panel 3**) there was a significant interaction effect (F = 2.3, df 10,164 p = 0.013). There were no group differences in terms of sleep satisfaction (**Figure 5.6: Panel 4**) clear-headedness on arising (**Figure 5.6: Panel 5**) or sleep latency (**Figure 5.6: Panel 6**).

5.4.8. Drug effects

Drug effects were measured on a scale of 0 – 4 with higher scores indicating greater severity. **Table 5.11** shows the mean and SEM for each item score over the study period.

Table 5.11 Drug effects

Item	Mirtazapine mean (SEM)	Modafinil mean (SEM)	*p*
Would you be willing to take it again?	2.4 (0.10)	2.6 (0.10)	*0.580*
Do you crave amphetamine?	2.0 (0.10)	2.0 (0.10)	*0.850*
Do you like the drug?	1.8 (0.10)	1.9 (0.09)	*0.568*
Would you be willing to pay for this drug?	1.7 (0.10)	1.5 (0.10)	*0.251*
Does the drug make you feel active, alert or energetic?	0.7 (0.10)	1.3 (0.10)	*0.005*
Do you feel stimulated?	0.7 (0.09)	0.6 (0.08)	*0.063*
Do you feel high?	0.7 (0.08)	0.3 (0.05)	*0.000*
Do you feel a rush?	0.6 (0.08)	0.1 (0.03)	*0.001*

Both medications were well tolerated with few positive subjective effects. Although scores were very low overall, subjects in the modafinil group felt significantly more active, alert or energetic in comparison to those receiving mirtazapine. Mirtazapine

treated subjects experienced a significantly greater 'rush' and 'high' in comparison to those treated with modafinil.

5.5. Discussion

The present study provides empirical evidence of safe, well tolerated and effective pharmacotherapies for acute amphetamine withdrawal treatment. These pilot trials showed that overall, modafinil was superior to mirtazapine, and both were superior to pericyazine (comparison group) in ameliorating the severity of acute amphetamine withdrawal symptoms in dependent amphetamine users undergoing inpatient treatment.

For the comparison group, the time course of the amphetamine withdrawal syndrome remained stable, and the severity of symptoms remained elevated overall, during inpatient treatment. This pattern of withdrawal symptoms contrasts with that shown by subjects in the first withdrawal study conducted two years previously (see **Chapter 2**) when withdrawal symptoms reduced over the first week of abstinence. Comparison of these two (treatment as usual) study samples showed no differences in demographic or substance use variables. However, an examination of in-treatment variables (data not shown) indicated that the present comparison group had significantly higher AWQ scores and had received significantly greater amounts of medication during withdrawal treatment. That is, the present group received significantly more benzodiazepines and pericyazine and were administered analgesia on more days during inpatient treatment. Given the similarity in demographic and substance use history for the two treatment as usual groups, it may be that the greater withdrawal severity seen in the present comparison group was related to the greater amounts of medication administered. Pericyazine, in common with other neuroleptics may produce dysphoria (for review see Voruganti & Awad, 2004) and this pharmacotherapeutic approach to amphetamine withdrawal treatment may require review.

Conversely, the overall severity of withdrawal symptoms in mirtazapine treated subjects was lower than that reported by comparison group subjects. However, like comparison group subjects, there was no significant decline in overall withdrawal symptom severity in mirtazapine treated subjects during the acute

withdrawal period. In contrast to this pattern, there was a significant decline in overall withdrawal severity in those who received modafinil treatment. However, by the end of the first week of abstinence, withdrawal severity was similar in both mirtazapine and modafinil treated subjects while scores remained elevated in the comparison group.

In comparison to treatment as usual, mirtazapine and modafinil were similarly effective in ameliorating the severity of depression-related symptoms (Component 3 of the ACSA) including anhedonia, poor concentration, depression, paranoid and suicidal ideation, motor retardation and inactivity. Additionally, depression-related symptoms in mirtazapine and modafinil treated subjects, but not comparison group subjects, declined significantly during the study period.

Differences between the three study groups on the hypersomnia subscale (Component 2) including symptoms of sleepiness and fatigue, were striking. However, while the comparatively lesser severity of sleepiness and fatigue in modafinil treated subjects was consistent with the wake-promoting actions of modafinil identified in earlier work (Boivin *et al.*, 1993; Besset *et al.*, 1996; Broughton *et al.*, 1997), the comparatively lower severity of anxiety and craving-related symptoms was less so. The effect of modafinil on symptoms such as anxiety, agitation, irritability, tension, craving and dreams (Component 1) has not been tested to date. It may be that fatigue and sleepiness had previously acted as interoceptive cues for amphetamine use and that the relative reduction in these symptoms, which occurred as a consequence of modafinil treatment, reduced the potency of these cues. Alternatively, it may be that in the comparative absence of fatigue and sleepiness, subjects receiving modafinil felt generally better and this was reflected in lower scores overall. However, the latter view is contradicted by the similar levels of general well-being in both modafinil and mirtazapine treated subjects.

The effectiveness of modafinil in ameliorating self-reported withdrawal severity was supported by independent observer-rated measures. However, the study drugs had no effect on the use of symptomatic medications. Subjects in all three groups received similar doses of benzodiazepines and were administered

analgesics on a similar number of days during withdrawal treatment. Moreover, study group membership had no effect on treatment retention.

Mirtazapine has sedating effects, which is why it is administered before retiring. Two subjects found the feelings of tiredness and lethargy aversive enough to refuse further medication and opt for treatment as usual with pericyazine. These sedating effects were reflected in the finding that mirtazapine treated subjects had relatively more hours of sleep (both day and night) during inpatient withdrawal treatment. However, drug effects on some sleep characteristics were also identified, with modafinil treated subjects having a greater depth of sleep with fewer night time awakenings in comparison to mirtazapine treated subjects. Morning dosing of modafinil was effective with no greater sleep latency and no greater use of sedation compared to those receiving mirtazapine. Moreover, no discontinuation effects for either drug were reported.

Both mirtazapine and modafinil were well tolerated with few positive subjective effects. Subjects in the modafinil group felt more active, alert or energetic while those receiving mirtazapine experienced a greater ‘rush’ and ‘high’. However, in both groups, scores for positive effects were very low. Other symptoms (in addition to those assessed by the study instruments) were mild and transient, responding readily to symptomatic medications. For subjects receiving mirtazapine, the most common ‘other’ symptom was that of aches and pains while for those receiving modafinil, headache was the most frequently reported symptom.

Study drop out numbers were similar for the mirtazapine and modafinil groups. Only one subject felt that modafinil was ‘ineffective’ and opted for treatment as usual with pericyazine. The view that modafinil had no discernable effects was commonly expressed by subjects receiving modafinil, although most opted to stay in the study. Despite their overall lower withdrawal severity, most subjects in the modafinil treated group expressed the view that modafinil had very little if any effect on their withdrawal symptoms and this is reflected in the similar scores for general well-being for the modafinil and mirtazapine treated subjects. However, to clinicians treating them, modafinil treated subjects appeared to be experiencing a significantly milder withdrawal syndrome in comparison to those receiving mirtazapine.

5.5.1. Limitations of the study

Two main factors should be taken into account when evaluating the findings of this study. Firstly, study groups were drawn from convenience samples enrolled sequentially rather than being randomly allocated. Additionally, study outcomes were assessed against an historical comparison group enrolled in a separate study evaluating the ACSA. Therefore, the comparison group did not provide information on drug effects or sleep patterns. Additionally, although treatment retention was a secondary outcome, the study was probably underpowered to detect a difference.

5.5.2. Summary and conclusions

This study provided empirical evidence of safe, well tolerated and effective pharmacotherapies for acute amphetamine withdrawal treatment. Of the two novel pharmacotherapies evaluated in this study, modafinil was shown to be more effective overall than mirtazapine in ameliorating symptoms of amphetamine withdrawal. Modafinil was particularly effective in ameliorating symptoms associated with anxiety, craving and fatigue, but had lesser efficacy in the treatment of depression-related symptoms. Both mirtazapine and modafinil were well tolerated with few positive subjective effects and there were no discontinuation symptoms when treatment was ceased at the end of the study period. Future studies should assess the efficacy of these medications in a randomised controlled design.

6. CHAPTER 6: SUMMARY AND CONCLUSIONS

Consistent with the first aim in this series of studies, an amphetamine withdrawal syndrome was quantified in dependant amphetamine users on cessation of regular amphetamine use. The first study, conducted in Australia, showed that the onset of withdrawal discomfort occurred within the first 24 hours following the last use of amphetamine, reaching a peak between 48 and 72 hours from the last use. More dependent subjects, with longer and heavier amphetamine use histories had a more severe withdrawal syndrome.

Craving for amphetamine remained elevated throughout the whole study period and unlike some other symptoms did not decline at any of the observed time points. Craving for carbohydrates, anhedonia, hypersomnia, tension, agitation and inactivity remained moderate to severe throughout the first week of abstinence. Anxiety and irritability peaked on the third day following the last use of amphetamine and although there was some decline in severity, both of these symptoms remained elevated relative to initial scores throughout the remainder of the study period.

Contrary to previous reports of a protracted course (Watson *et al.*, 1972; Rawson *et al.*, 2002), mood-related symptoms of depression and fatigue peaked and declined within the first week of abstinence. Symptoms such as increased appetite, motor retardation and difficulty concentrating were all moderately elevated and relatively stable over the study period. Levels of paranoid and suicidal ideation, and decreased appetite were low, remaining stable throughout. Unlike cocaine withdrawal (Kampman *et al.*, 1998), bradycardia was not a feature of amphetamine withdrawal, at least in the present sample.

A ‘crash’ period characterised by relative oversleeping for around three days following the last use of amphetamine was identified. Additionally, several sleep characteristics such as clearheadedness on arising, depth, quality and satisfaction with night sleep improved rapidly following admission, remaining stable and at moderate levels during the first week of abstinence. There was a marked increase in total hours of sleep between pre-admission and the peak at day two when subjects slept for around 14 hours. Thereafter, hours of sleep gradually declined,

remaining stable at around eight hours per night. Unlike previous studies (Gossop *et al.*, 1982), there was no insomnia following this period of oversleeping – at least during the eight day period covered by the study reported in **Chapter 2**.

Consistent with other samples of amphetamine users (Hawks *et al.*, 1969), reduced hours of sleep were reported in the week prior to interview – probably reflecting the stimulant properties of amphetamine used in that time period. The lack of any identified relationship between the number of hours of sleep in the week prior to admission and hours of sleep during the first week of abstinence is consistent with previous reports (Angrist & Sudilovsky, 1978) which found that even where patients reported sufficient sleep, they were still fatigued for several days in the early phase of abstinence. Therefore, the evidence to date suggests that the oversleeping characteristic of early amphetamine abstinence is not simply a rebound response to a period of relative sleep deprivation and requires further investigation.

While there were modest relationships between observer-rated assessments of withdrawal symptoms and night time sleep duration, no objective measures of amphetamine withdrawal were identified. Unlike the signs identified as characteristic of alcohol (White *et al.*, 1994) or opioid withdrawal (Handelsman *et al.*, 1987), there were no directly measurable amphetamine withdrawal signs.

The duration of the assessment period was extended in a second amphetamine withdrawal study conducted in Thailand. In this study, the natural history of amphetamine withdrawal during the first three weeks of abstinence was quantified and the results compared to similar data from a group of age and sex matched normal, healthy individuals. This study confirmed the first week of abstinence as the period of greatest withdrawal severity. However, a somewhat different pattern of withdrawal symptoms was identified in the Thai subjects in comparison to that observed in the Australian study. In the Thai study, overall symptom severity declined from a high initial peak within 24 hours of the last use of amphetamines, reducing to near comparison group levels by about the end of the first week of abstinence. Two phases were identified: an acute phase that occurred during the first week of abstinence, and a sub-acute phase lasting for at least two further

weeks. As for the first study, withdrawal severity was greater in those subjects who were older, more dependent and who had been using amphetamine longer.

In the Thai study, the amphetamine withdrawal syndrome was characterised principally by increases in sleeping and appetite. A cluster of depression-related symptoms including inactivity, fatigue, anhedonia, and dysphoria were marked during the first week, but had largely resolved by the end of the acute phase of abstinence. Anxiety, motor retardation, agitation, vivid dreams, amphetamine craving, poor concentration, irritability, and tension were less severe symptoms. Of the withdrawal symptoms measured, most had reduced towards comparison group levels by the end of the first week of abstinence. Exceptions included the sleep and appetite related symptoms that persisted through weeks two and three of abstinence (the sub-acute phase).

As in the Australian study, there was a marked increase in total hours of sleep between pre-admission and the peak at day five when subjects slept for around 11 hours. This peak was later than that observed for the Australian sample and may have been a function of sedation administered to the latter group. However, in common with the Australian sample, there was no insomnia following the ‘crash’ despite the lack of sedation. Instead, hours of sleep gradually declined from their peak until the ninth day, after which total hours of sleep remained stable at around nine hours for the rest of the three week monitoring period.

However, the quality and depth of sleep in patients undergoing withdrawal treatment decreased at the end of the acute phase and did not return to previous levels until the third week of abstinence. Therefore, while Thai subjects had a greater total amount of sleep, in contrast to comparison group members, their sleep patterns were of a poorer quality as they took significantly longer to fall asleep and had a greater number of awakenings during the night. Additionally, clearheadedness on arising did not reach comparison group levels until about the middle of the second week of abstinence.

In terms of sleep duration, the findings from the present Australian and Thai studies of amphetamine withdrawal contrast with an earlier investigation into sleep duration in hospitalised amphetamine users in the United Kingdom (UK) (Gossop

et al., 1982). This study showed that in comparison to controls, the number of hours of night time sleep was significantly less in the amphetamine users over the 20 day study period. While hours of sleep for amphetamine users were greater than or similar to controls on nights 1 – 5 of admission, amphetamine users slept less than controls on nights 6 – 20 when the UK study ended. These authors suggested that withdrawal insomnia may be dose-related. The identification (in the Thai sample) of the cost of amphetamine used in the month prior to admission and the length of regular use as significant positive predictors of sleep during withdrawal supported this contention. An analysis of the predictors of sleep patterns was not conducted in the Australian study because of the administration of anxiolytics and sedatives in this sample.

No directly measurable amphetamine withdrawal signs were identified in either the Australian or the Thai samples. Objective measures such as pulse and blood pressure remained within normal limits for the duration of the study period. However, the moderately strong relationship between subjective withdrawal symptoms and the observer-rated evaluation of withdrawal severity confirmed that experienced clinicians are able to provide a reasonably accurate and consistent judgement as to the current level of discomfort experienced by patients in treatment for amphetamine withdrawal. Additionally, the number of hours of sleep provides an observable indication of the time course and severity of withdrawal.

Although almost three-quarters of the inpatient subjects in the Thai study were moderately or severely depressed on admission for treatment, the proportion of subjects falling into these categories had reduced to less than one-third by the beginning of the second week of abstinence and to less than one-quarter by the beginning of the third week. As for the first withdrawal study, these findings do not support previous studies showing prolonged depression following cessation of dependent amphetamine use (Watson *et al.*, 1972; Rawson *et al.*, 2002).

While there were substantial differences in self-reported withdrawal severity between the Australian and Thai amphetamine users, differences in demographic, cultural and substance use variables precluded direct comparison of these two samples. However, regression analyses of the combined Australian and Thai data identified the severity of dependence as the strongest predictor of self-reported

withdrawal severity, with length of regular amphetamine use and days of amphetamine use in the previous month contributing a relatively weaker, but still significant proportion of the variance in scores. In contrast, study membership was the weakest of the four independent variables, contributing little to perceptions of withdrawal severity. This suggested that the substantial difference in self-reported withdrawal severity is less a function of cultural group than the intensity of amphetamine dependence and the duration and intensity of exposure to amphetamines.

Consistent with the second aim of this study, the Amphetamine Cessation Symptom Assessment (ACSA) scale was developed and assessed as a reliable and valid instrument for the measurement of amphetamine withdrawal symptoms in newly abstinent amphetamine users. The ACSA was based on two existing scales of known reliability and validity, the AWQ (Srisurapanont *et al.*, 1999) and a form of the CSSA modified for use with amphetamine users (Kampman *et al.*, 1998). These two scales were used in both the Australian and Thai amphetamine withdrawal studies and data from both studies were combined to form the basis for the new instrument.

Reliability and principal components analysis of data from the AWQ and the ASSA facilitated item selection leading to the exclusion of six poorly performing items – five from the ASSA and one from the AWQ. After the removal of duplicated items, 16 items were incorporated into the new scale. For convenience, the response format and design for the ACSA was based on an established opiate withdrawal instrument, the Subjective Opiate Withdrawal Scale (Handelsman *et al.*, 1987).

As amphetamine withdrawal symptoms are largely subjective, the ACSA was designed to be self-completed, thereby avoiding any bias associated with inter-rater variability. The time scale referred to the previous 24-hours making the instrument suitable for once a day administration and convenient for both clinical use and research purposes. Therefore, the ACSA was designed to strike a balance between efficiency and reliability by retaining the minimum number of items consistent with the accurate measurement of the construct, i.e. amphetamine withdrawal (Smith & McCarthy, 1995).

A new sample of treatment-seeking amphetamine users were recruited to provide reliability and validity data for the ACSA. This analysis showed that the structure of the ACSA could be clarified through psychometric analysis. Content validity for the new instrument had already been established through the adoption of items from validated instruments such as the AWQ and the CSSA (Straub, 1989). The suitability of the new instrument for use in amphetamine withdrawal was confirmed by the high rate of endorsement observed.

Reliability analysis indicated a satisfactory level of internal consistency for the ACSA that was suggestive of unidimensionality. However, a principal components analysis followed by oblique rotation showed that amphetamine withdrawal was not unidimensional and that a three-factor solution provided a good fit to the data with all items being assigned to a factor. The strongest factor comprising seven items was labelled ‘Anxiety and Craving’. Items loading on this factor included craving frequency and intensity, agitation, irritability, tension, anxiety and vivid, unpleasant dreams. The second component, ‘Hypersomnia’ comprised fatigue and hypersomnia items and the third factor labelled ‘Depression’ comprised seven items assessing suicidal ideation, anhedonia, depression, paranoid ideation, poor concentration, inactivity and motor retardation.

Analogue factor scores were computed for each factor by summing the actual values of the ACSA items loading on each factor. These analogue factor scores were designated as subscales in subsequent analyses. This technique also has the advantage of producing scores that can be calculated easily by clinicians and is justifiable in terms of the structure exhibited in the factor analysis. Reliability analysis for the three scale components was satisfactory, suggesting that the three components were each unidimensional.

The strong positive correlation between the new instrument and an established one (the AWQ) provided good evidence for concurrent validity (Kline, 1998). Further evidence of convergence was provided by the modest but significant positive relationship between the ACSA and an alternative method of evaluating the same construct such as observer-rated withdrawal severity (Foster & Cone, 1995). Positive relationships between the ACSA (aggregate and factor scores), criteria such as the number of days on which amphetamine had been used, total

grams used, the cost of amphetamine, and the level of amphetamine dependence provided evidence of criterion-related validity.

Treatment completers had significantly lower ACSA scores in comparison to those who left treatment early thus providing evidence of predictive validity for the new instrument. Furthermore, treatment completers had significantly lower 'Anxiety and Craving' and 'Depression' scores in comparison to non-completers. Of the three components, only 'Hypersomnia' did not show predictive validity. Thus, elevated affective and mood related symptoms rather than fatigue and sleep related symptoms may increase the likelihood of treatment drop out in patients undergoing amphetamine withdrawal treatment.

Higher total ACSA and 'Anxiety and Craving' scores were associated with a reduction in the quality of several sleep characteristics. Specifically, greater sleep latency and night time awakenings, reduced hours of sleep during the night, reduced sleep quality, depth and satisfaction, and reduced clearheadedness on awakening. As expected, higher scores for the 'Hypersomnia' subscale were associated with greater hours of sleep and less clearheadedness on arising. Higher 'Depression' scores were associated with reductions in clearheadedness on arising, sleep satisfaction and sleep quality as well as increased sleep latency and number of awakenings during the night. Therefore, while different sleep characteristics were associated with different ACSA subscales, there was substantial overlap.

The three factor structure found in the original study of the AWQ by Srisurapanont and colleagues (Srisurapanont *et al.*, 1999) was not replicated in the present factor analyses of the AWQ. There may be several reasons for this lack of replication. Firstly, the original AWQ study measured withdrawal severity in Thai amphetamine users of around 20 years of age who had been either swallowing or smoking amphetamines for around two years. All were currently undergoing inpatient amphetamine withdrawal treatment and all had been abstinent from amphetamines for between one and five days. In contrast, the present data set included a broader range of subjects, many of whom had administered amphetamines by injection, were older and had been using amphetamines longer, all of which may have influenced the factor loadings of the AWQ.

Having identified and quantified a two-phase amphetamine withdrawal syndrome and developed a reliable and valid instrument for its measurement, the third aim of this series of studies was addressed. Results of this final study provided the first empirical evidence of safe, well tolerated and potentially effective pharmacotherapies for acute amphetamine withdrawal treatment. These pilot pharmacotherapy trials showed that overall, the wake-promoting drug modafinil was superior to the serotonin and noradrenaline reuptake inhibitor antidepressant mirtazapine in ameliorating the severity of acute amphetamine withdrawal symptoms in dependent amphetamine users undergoing inpatient treatment. Moreover, both modafinil and mirtazapine had greater efficacy in amphetamine withdrawal compared to treatment as usual with the dopamine antagonist pericyazine (comparison group).

For the comparison group, the time course of the amphetamine withdrawal syndrome remained stable, and the severity of withdrawal symptoms remained elevated overall, during inpatient treatment. This pattern of withdrawal symptoms contrasted with that shown by subjects in the first Australian withdrawal study (conducted two years previously) when withdrawal symptoms reduced over the first week of abstinence. Comparison of these two (treatment as usual) study samples showed no differences in demographic or substance use variables. However, an examination of in-treatment variables indicated that the later group had significantly higher AWQ scores and had received significantly greater amounts of medication during withdrawal treatment. That is, the later group received significantly more benzodiazepines and pericyazine and were administered analgesia on more days during inpatient treatment. Given the similarity in demographic and substance use history for the two treatment as usual groups, it may be that the greater withdrawal severity seen in the later group was related to the greater amounts of medication administered. Pericyazine, in common with other neuroleptics may produce dysphoria (Voruganti & Awad, 2004) and this pharmacotherapeutic approach to amphetamine withdrawal treatment may require review.

Conversely, the overall severity of withdrawal symptoms in mirtazapine treated subjects was lower than that reported by comparison group subjects. However,

like comparison group subjects, there was no significant decline in overall withdrawal symptom severity in mirtazapine treated subjects during the acute withdrawal period. In contrast to this pattern, there was a significant decline in overall withdrawal severity in those who received modafinil treatment. However, by the end of the first week of abstinence, withdrawal severity was similar in both mirtazapine and modafinil treated subjects, while scores remained elevated in the comparison group. In comparison to treatment as usual, mirtazapine and modafinil were similarly effective in ameliorating the severity of depression-related symptoms. Additionally, depression-related symptoms in mirtazapine and modafinil treated subjects, but not comparison group subjects, declined significantly during the study period.

Differences between the three study groups on the Hypersomnia subscale were marked. However, while the comparatively lesser severity of sleepiness and fatigue in modafinil treated subjects was consistent with the wake-promoting actions of modafinil identified in earlier work (Boivin *et al.*, 1993; Besset *et al.*, 1996; Broughton *et al.*, 1997), the comparatively lower severity of anxiety and craving-related symptoms was less so. The effect of modafinil on symptoms such as anxiety, agitation, irritability, tension, craving and dreams (the Anxiety and Craving Subscale) has not been investigated to date. It may be that fatigue and sleepiness had previously acted as interoceptive cues for amphetamine use and that the relative reduction in these symptoms, which occurred as a consequence of modafinil treatment, reduced the potency of these cues. Alternatively, it may be that in the comparative absence of fatigue and sleepiness, subjects receiving modafinil felt generally better and this was reflected in lower scores overall. However, the latter view is contradicted by the similar levels of general well-being in both modafinil and mirtazapine treated subjects.

The effectiveness of modafinil in ameliorating self-reported withdrawal severity was supported by independent observer-rated measures. However, none of the three study medications influenced the use of symptomatic medications. Subjects in all three groups received similar doses of benzodiazepines and were administered analgesics on a similar number of days during withdrawal treatment. Moreover, study group membership had no effect on treatment retention.

Mirtazapine has sedating effects, which is why it is administered before retiring. Two subjects found the feelings of tiredness and lethargy aversive enough to refuse further medication and opt for treatment as usual with pericyazine. These sedating effects were reflected in the finding that mirtazapine treated subjects had relatively more hours of sleep (both day and night) during inpatient withdrawal treatment. However, drug effects on some sleep characteristics were also identified, with modafinil treated subjects having a greater depth of sleep with fewer night time awakenings in comparison to mirtazapine treated subjects. Morning dosing of modafinil was effective with no greater sleep latency and no greater use of sedation compared to those receiving mirtazapine.

Both mirtazapine and modafinil were well tolerated with few positive subjective effects. Subjects in the modafinil group felt more active, alert or energetic while those receiving mirtazapine experienced a greater 'rush' and 'high'. However, in both groups, scores for positive effects were very low. Other symptoms (in addition to those assessed by the study instruments) were mild and transient, responding readily to symptomatic medications. For subjects receiving mirtazapine, the most common 'other' symptom was that of aches and pains while for those receiving modafinil, headache was the most frequently reported symptom. Importantly, there were no discontinuation effects for either drug.

Study drop out numbers were similar for the mirtazapine and modafinil groups. Only one subject felt that modafinil was 'ineffective' and opted for treatment as usual with pericyazine. The view that modafinil had no discernable effects was commonly expressed by subjects receiving modafinil, although most opted to stay in the study. Despite their overall lower withdrawal severity, most subjects in the modafinil treated group expressed the view that modafinil had very little if any effect on their withdrawal symptoms and this is reflected in the similar scores for general well-being for the modafinil and mirtazapine treated subjects. However, to clinicians treating them, modafinil treated subjects appeared to be significantly less unwell in comparison to those receiving mirtazapine. Additionally, when specific withdrawal symptoms were assessed by use of instruments like the ACSA, significant differences were identified.

Therefore, the time course and severity of amphetamine withdrawal as determined by the results of the present series of studies was consistent with several aspects of previous clinical reports. That is, in agreement with naturalistic observation of patients undergoing amphetamine withdrawal, the process was characterised by oversleeping and a cluster of mood and affective symptoms, particularly in the first week of abstinence. The amphetamine users assessed in the present work showed marked levels of depression on treatment entry that had largely resolved by the end of the first week of abstinence. However, the rapid resolution of depressive symptoms may have been mediated by the inpatient setting which to some extent insulated subjects from the cues and stressors experienced in the external community. With the exception of those treated with modafinil, amphetamine dependent subjects in all of the studies reported in this body of work experienced a 'crash' during the first week which was unrelated to pre-admission hours of sleep. However, unlike some reports, there was no post-crash insomnia.

An interesting finding of the present work was the exacerbation of withdrawal symptomatology in those subjects who had received greater amounts of medication during withdrawal treatment despite a similar demographic and drug use background. This suggested that the use of medications such as benzodiazepines and dopamine antagonists may exacerbate symptoms of amphetamine withdrawal and points to the need for careful evaluation of pharmacotherapies prior to their use as a clinic standard.

6.1. Limitations of the studies

Several factors should be taken into account when evaluating the findings of these studies. Firstly, study groups were drawn from convenience samples of treatment-seeking amphetamine users, the majority of whom where severely dependent and long-term amphetamine users. Additionally, given that the study setting was an inpatient treatment facility, the absence of conditioned cues for amphetamine use may have reduced the frequency and intensity of subjective craving phenomena. Therefore, these results may not generalise to community samples of less severely dependent amphetamine users.

An important issue in interpreting the results of the first Australian withdrawal study was the use of psychoactive medication to ameliorate withdrawal symptoms. Use of medication may have masked some withdrawal symptoms, particularly insomnia. For the Thai withdrawal study, comparison group participants, who were seen daily at their place of work or study, were not tested under exactly the same conditions as inpatients.

To conduct the psychometric evaluation of the ACSA, 107 subjects provided a total of 302 questionnaires for analysis. This sample size is considered adequate to test a 16 item instrument (Feinstein, 1987) and complies with the minimum sample size requirement of 100 subjects when testing a new instrument (Norman & Steiner, 1994). However, when conducting the psychometric evaluation of a new instrument, particularly where factor analysis is used, bigger is always considered better in terms of sample size (Kline, 1998; Tabachnick & Fidell, 2001; Kline, 2002). A replication of the ACSA factor structure in a larger sample would provide confirmation of the psychometric structure revealed in the present analysis.

As for the previous studies, subjects in the pharmacotherapies trials were enrolled sequentially rather than being randomly allocated. Furthermore, outcomes were assessed against an historical comparison group enrolled in a separate study evaluating the ACSA. Therefore, the comparison group did not provide information on drug effects or sleep patterns. Additionally, although treatment retention was a secondary outcome, the study was probably underpowered to detect a difference.

6.2. Conclusions

Withdrawal from amphetamine in dependent users can precipitate a range of aversive, although not life-threatening symptoms, that occur (in a dose-dependent manner) mainly during the first week of abstinence. Many of these symptoms are the converse of the direct effects of amphetamines and can be conceptualised as rebound phenomena. One exception is the withdrawal ‘crash’ or oversleeping that does not seem to be simply a function of recent sleep deprivation. While the withdrawal symptoms are largely subjective, experienced clinicians can make an assessment of withdrawal severity based on signs such as the number of hours of sleep.

It is during the first week of abstinence that the need for pharmacological treatment of these symptoms is greatest and several are amenable to pharmacological intervention. However, medications designed to treat particular withdrawal symptoms may exacerbate others. For example, dopamine antagonists such as pericyazine administered for the treatment of agitation may increase dysphoria and fatigue. Many of the symptoms experienced e.g., anxiety and depression-related symptoms, and sleep disturbances are common to withdrawal from other psychoactive substances and no sign or symptom exclusive to amphetamine withdrawal has been identified to date.

It may be that such symptoms are (at least to some extent) a function of situational factors rather than specific withdrawal symptoms – particularly in treatment samples. That is, many users enter treatment at a time of crisis and may be concerned about a range of financial, legal and/or relationship problems during treatment. Other variables that may influence the experience of withdrawal include expectancies regarding the duration and severity of symptoms, psychiatric or medical illnesses and the setting in which withdrawal occurs. Substance-related variables that may influence the experience of amphetamine withdrawal include the route of administration, the potency of amphetamine used and dependence on other psychoactive drugs. Therefore, while the work in this thesis has described the first steps in the systematic characterisation of the amphetamine withdrawal syndrome, a number of other potential influences on the experience of amphetamine withdrawal await exploration in the future.

6.3. Future directions

Further validation studies of the ACSA in different populations of amphetamine users may reveal a different pattern of symptoms to that of the present severely dependent inpatient samples. Validation of the ACSA in community samples with lower levels of amphetamine dependence would be an important step in the evaluation of interventions aimed at reducing amphetamine-related harms at an earlier stage of amphetamine use.

A stepped-care approach to amphetamine dependence whereby the level of intervention is titrated to the intensity of amphetamine use and degree of

depression has recently been recommended (Baker *et al.*, 2005). Using this approach, patients may receive a range of interventions based on their mood state and substance use history. These interventions may involve a relatively brief period of assessment, education and monitoring for those with low levels of use and depression, while patients with higher levels of depression and/or greater intensity of amphetamine use may receive two to four CBT sessions. Severely dependent and/or depressed patients may require long term psychotherapy and/or pharmacotherapy. While this approach was developed in non-treatment seeking samples, the model could be adapted for use in in-patient settings.

A major finding of the present series of studies was the identification of modafinil as a potentially useful pharmacotherapy for amphetamine withdrawal. Having established the safety of modafinil in amphetamine withdrawal, a logical next step would be to replicate the study with a larger sample that included a placebo control. A larger sample would provide further evidence of the safety and efficacy of modafinil in amphetamine dependence treatment and would also provide adequate power to assess other factors such as retention in treatment and the effect of depression on response to treatment. The design could be further refined to include an assessment of different dose levels. The identification of the optimal dose of modafinil consistent with clinical and statistical significance in ameliorating amphetamine withdrawal symptoms would be beneficial as there are substantial costs associated with modafinil treatment and it is possible that a smaller dose (i.e., 200mg per day) would be as effective. Therefore, as well as identifying the optimal dose of modafinil, a successful dose-ranging study may have economic benefits in terms of reduced medication costs. The identification of an effective pharmacotherapy that would ameliorate the acute withdrawal symptoms experienced by dependent users on cessation of use would be of considerable benefit to patients and their treating clinicians.