1. CHAPTER 1: INTRODUCTION

1.1. Definition of terms

The term 'amphetamines' generally refers to a group of chemically related synthetic substances, including amphetamine and methamphetamine and derivatives such as 3,4 methylene-dioxy-methamphetamine (MDMA). The present work is concerned with the effect of amphetamine and methamphetamine but excluding derivatives such as MDMA. Throughout this document, except where the substance is known to be methamphetamine, the term amphetamine will be used to describe both amphetamine and methamphetamine.

1.2. Study rationale

This work was conducted with the principal objective of addressing the need for empirical data regarding the nature of the amphetamine withdrawal syndrome and using this information to develop effective treatment approaches to ameliorate these symptoms.

The nature of the withdrawal syndrome from other psychoactive substances e.g., alcohol (Sullivan, Swift & Lewis, 1991; White, Frewin, Kaur, Flavel & McGregor, 1994); opioids (Bradley, Gossop, Phillips & Legarda, 1987; Handelsman, Cochrane, Aronson, Ness, Rubinstein & Kanof, 1987; Gossop, 1990); nicotine (Jorenby, Hatsukami, Smith, Fiore, Allen, Jensen & Baker, 1996; Kenny & Markou, 2001); benzodiazepines (Busto, Sykora & Sellers, 1990; Tyrer, Murphy & Riley, 1990; Couvee & Zitman, 2002; McGregor, Machin & White, 2003); cocaine (Weddington, Brown, Haertzen, Cone, Dax, Herning & Michaelson, 1990; Satel, Price, Palumbo, McDougle, Krystal, Gawin, Charney, Heninger & Kleber, 1991) and marijuana (Budney, Novy & Hughes, 1999; Budney, Moore, Vandrey & Hughes, 2003) has been measured systematically. However, as noted by two recent major reviews (Srisurapanont, Jarasuraisin & Kittiratanapaiboon, 2003; Baker, Lee & Jenner, 2004), little work has addressed the systematic measurement and treatment of withdrawal from the amphetamines. 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, Hando, Darke & Ross, 1996; Vincent, Shoobridge, Ask, Allsop & Ali, 1998; Byqvist, 1999; Wright & Klee, 2001; Brecht & Greenwell, 2002).

1.3. Development and early use of the amphetamines

Amphetamines are potent central nervous system stimulants with sympathomimetic and adrenergic agonist activity. They were first synthesised in 1887 and their sympathomimetic and respiratory stimulant effects described in the1930s (Piness, Miller & Alles, 1930; Alles, 1933; Alles & Prinzmetal, 1933). The administration of amphetamines increases mood, arousal and activity (Silverstone, Fincham, Wells & Kyriakides, 1980; Miller & Miller, 1983; Zacny & de Wit, 1989; de Wit, Clark & Brauer, 1997) and produces an increase in heart rate and blood pressure (Brauer, Ambre & De Wit, 1996; de Wit *et al.*, 1997; Wachtel & de Wit, 1999; Johnson, Ait-Daoud & Wells, 2000; Drevets, Gautier, Price, Kupfer, Kinahan, Grace, Price & Mathis, 2001). Their stimulant and anorectic properties led to wide use of the amphetamines for a range of therapeutic indications (e.g. the treatment of obesity and narcolepsy) and for recreational or nonmedical purposes such as the enhancement of sports performance (Jones & Pichot, 1998; Bowers, 2002) and to alleviate fatigue in a range of situations e.g., long distance truck drivers, chefs, shift workers and students (Baker, Gowing, Lee & Proudfoot, 2004).

1.4. Development of controls on amphetamine use

As the rate of amphetamine use increased, evidence for their dependence potential emerged and their use evolved into a public health problem. In response to concerns regarding the widespread use and potential harms associated with amphetamines (particularly non-medical use), strict control measures, similar to those for narcotics were applied by international consensus in 1971 (Yoshida, 1997). Restrictions on the availability of amphetamines led to the development of clandestine laboratories to meet demand. Illicit amphetamines were manufactured from precursor chemicals that were diverted from pharmaceutical companies,

chemists and doctors to supply a market in illicit amphetamine distribution which occurred through criminal networks (Anglin, Burke, Perrochet, Stamper & Dawad-Noursi, 2000). The growth of an illicit amphetamine market led in turn to increased law enforcement efforts to combat illegal production and use of these substances.

1.5. Epidemiology of illicit amphetamine use

Historically, illicit amphetamine use has formed a pattern of 'epidemics' in different countries. For example, until they were withdrawn from the market, inhaler preparations of amphetamines were widely used for non-medical purposes in the United States during the 1940's (Grinspoon & Bakalar, 1977), while in post World War II Japan, there was an amphetamine epidemic which lasted until the middle of the 1950's (Grinspoon & Hedblom, 1975). A review by Hall and Hando showed that epidemics of amphetamine use have also occurred in Sweden during the 1940s, 1950s and 1960s, the United States in the late 1960s and early 1970s, and Britain in the late 1950s and late 1960s. Illicit amphetamine use increased again in Japan in the 1970s (Hall & Hando, 1993). Recent reports have indicated that amphetamine use has reached epidemic proportions in large parts of the Western and Midwestern United States (Rawson, Anglin & Ling, 2002). Additionally, the South-East Asian region has seen an increase in the production and consumption of amphetamine, particularly in Thailand (Cheurprakobkit, 2000; National Household Survey Thailand, 2001; Bureau for International Narcotics and Law Enforcement Affairs, 2002; Ahmad, 2003).

The use of amphetamines is also common in Australia. National surveys have shown that amphetamines are (after cannabis) the second most commonly used illicit drug in Australia (Australian Institute of Health and Welfare, 2003). Moreover, their use is widespread and increasing (Topp, Degenhardt, Kaye & Darke, 2002; Australian Illicit Drug Report, 2003). This increase is reflected in increased numbers of amphetamine users presenting for treatment (Copeland & Sorensen, 2001).

A number of sources have identified methamphetamine as being the most common form of amphetamine currently used in the Australasian region (Bureau for International Narcotics and Law Enforcement Affairs, 2002; Australian Illicit

Drug Report, 2003; United Nations Office on Drugs and Crime, 2003). Most of the amphetamine seized by law enforcement officials in Australia during the period 1997 – 2002 was methamphetamine (97% of seizures) while the average purity of seized methamphetamine increased from around 11% in 1997/98 to around 22% in 2000/2001 (McKetin & McLaren, 2004).

1.6. Mechanism of action of amphetamines

Methamphetamine and its principle metabolite, amphetamine are indirectly acting sympathomimetic drugs that interact with amine systems in the brain and the peripheral nervous system to produce a wide range of effects on physiology and behaviour. To produce these effects, amphetamines act at a number of sites on the presynaptic neuron to increase extracellular, relative to intracellular, concentrations of three neurotransmitters: dopamine, noradrenaline and serotonin (Seiden, Sabol & Ricaurte, 1993; Kuczenski & Segal, 1997; Rothman, Partilla, Baumann, Dersch, Carroll & Rice, 2000). Amphetamines inhibit the uptake of these neurotransmitters into the presynaptic neuron by inhibiting the action of the relevant transporter on the membranes of dopaminergic, serotonergic and adrenergic neurons (Seiden *et al.*, 1993; Rothman, Baumann, Dersch, Romero, Rice, Carroll & Partilla, 2001; Fleckenstein & Hanson, 2003).

As well as inhibiting uptake, amphetamine can reverse the action of the transporters so that they facilitate neurotransmitter movement across the membrane and into the synaptic cleft (Kuczenski, 1983; Kuczenski, Segal, Cho & Melega, 1995; Amara & Sonders, 1998; Kahlig & Galli, 2003; Khoshbouei, Wang, Lechleiter, Javitch & Galli, 2003). Additionally, amphetamine displaces newly synthesised neurotransmitters from their respective vesicular stores by acting on the vesicular monoamine transporter, thus increasing the pool of cytoplasmic transmitter available for release. Amphetamines can also inhibit the metabolism of these neurotransmitters by inhibiting the action of monoamine oxidase (Seiden *et al.*, 1993). Recent work using in vitro methods has quantified the effects of amphetamine and methamphetamine as reuptake inhibitors and substrate-type releasers (Rothman *et al.*, 2000; Rothman *et al.*, 2001). **Table 1.1** shows the effects of amphetamine and methamphetamine on the release of serotonin (5-hydroxytriptamine; 5-HT) noradrenaline and dopamine (Rothman *et al.*, 2001).

Table 1.1   Neurotransmitter release and uptake inhibition

	NA		5-HT		DA	
	Release IC$_{50}$ nM (SD)	Uptake Ki Nm (SD)	Release IC$_{50}$ nM (SD)	Uptake Ki nM (SD)	Release IC$_{50}$ nM (SD)	Uptake Ki nM (SD)
MTH*	12.3 (0.7)	48.0 (5.1)	736 (45)	2137 (98)	24.5 (2.1)	114 (11)
AMP	7.07 (0.95)	38.9 (1.8)	1765 (94)	3830 (170)	24.8 (3.5)	34 (6)
NA	164 (13)	63.9 (1.6)	>10,000	>50,000	869 (51)	357 (27)
DA	66.2 (5.4)	40.3 (4.4)	>10,000	6489 (200)	86.9 (9.7)	38.3 (1.6)
5-HT	>10,000	3013 (266)	44.4 (5.3)	16.7 (0.9)	>10,000	2703 (79)

Data in Table 1.1 derived from (Rothman *et al.*, 2001) page 37.

*Methamphetamine (MTH) Amphetamine (AMP) Noradrenaline (NA)
Dopamine (DA) 5-Hydroxytryptamine (5-HT)

Both methamphetamine and amphetamine are potent releasers of noradrenaline and dopamine and relatively weak releasers of serotonin. While methamphetamine and amphetamine are equally potent as dopamine and noradrenaline releasers, methamphetamine is approximately 2.5 times more potent as a serotonin releaser in comparison to amphetamine, but both drugs have relatively weak serotonergic effects (Rothman & Bauman, 2002). In summary, there are three principal processes underlying the mechanism of action of amphetamines at the neuronal level – release, uptake and enzymatic inactivation of neurotransmitters.

1.7.   Amphetamine pharmacokinetics

Amphetamines are weak bases with a pKa around 9.9, a low molecular weight, low protein binding (around 20%) and a moderately high volume of distribution (de la Torre, Farre, Navarro, Pacifici, Zuccaro & Pichini, 2004). Both methamphetamine and amphetamine are readily absorbed from the gastrointestinal tract and the nasal mucosa and freely penetrate the blood brain

barrier (Pichini, Altieri, Zuccaro & Pacifici, 1996; Cho & Melega, 2002; Harris, Boxenbaum, Everhart, Sequeira, Mendelson & Jones, 2003). Both are mainly excreted unchanged in the urine via the organic cation transport system (Sakai, Niwaguchi, Kimura & Murata, 1985; Cook, Jeffcoat, Hill, Pugh, Patetta, Sadler, White & Perez-Reyes, 1993). Via this route, amphetamines are excreted more rapidly in an acidic environment (Oyler, Cone, Joseph, Moolchan & Huestis, 2002).

In addition to elimination of unchanged drug via the urine, both amphetamine and methamphetamine are metabolised by Phase I (oxidation) and Phase II (conjugation) reactions. In Phase I metabolism, both amphetamine and methamphetamine – as substrates for the cytochrome P450 systems – undergo N-dealkylation and hydroxylation reactions. One of the cytochrome P450 systems responsible for these reactions in humans is CYP2D6 (Lin, Di Stefano, Schmitz, Hsu, Ellis, Lennard, Tucker & Cho, 1997; Wu, Otton, Inaba, Kalow & Sellers, 1997; Bach, Coutts & Baker, 1999). However, around 7 – 10 percent of the Caucasian population lack this enzyme and are designated poor metabolisers in comparison to the rest of the population (extensive metabolisers). Thus, the capacity of the individual to biotransform amphetamine mediates the disposition and action of these compounds depending on the individual phenotype (Kroemer & Eichelbaum, 1995).

1.7.1. Route of administration

While oral administration has traditionally been the route of choice for the administration of amphetamines, in recent years both injection and inhalation of vapour (smoking) from heated amphetamine have become more common modes (Perez-Reyes, White, McDonald, Hill, Jeffcoat & Cook, 1991; Cook *et al.*, 1993; Cheurprakobkit, 2000; National Household Survey Thailand, 2001; Bureau for International Narcotics and Law Enforcement Affairs, 2002; Cho & Melega, 2002; Ahmad, 2003; Degenhardt & Topp, 2003; Humeniuk & Ali, 2004).

1.7.1.1. Oral administration

Both methamphetamine and amphetamine are absorbed after oral ingestion with peak plasma concentrations occurring at 2 – 4 hours (Angrist, Corwin, Bartlik & Cooper, 1987; Perez-Reyes, White, McDonald, Hicks, Jeffcoat, Hill & Cook, 1991;

Brauer *et al.*, 1996; Asghar, Tanay, Baker, Greenshaw & Silverstone, 2003; Schepers, Oyler, Joseph, Cone, Moolchan & Huestis, 2003). Maximum cardiovascular effects of orally administered amphetamine occur at one hour and maximum observer-rated activation and subjective effects at 1½ to 2 hours post-ingestion. However, after reaching a peak, subjective and behavioural effects decline despite substantial amphetamine concentrations suggesting the development of acute tolerance (Angrist *et al.*, 1987; Brauer *et al.*, 1996). Following oral administration, the oral bioavailability of methamphetamine is around 67% (Cook *et al.*, 1993) and the elimination half-life around 10 hours (Cook, Jeffcoat, Sadler, Hill, Voyksner, Pugh, White & Perez-Reyes, 1992).

1.7.1.2.   *Intravenous use and smoking of amphetamines*

As noted above, both vapour inhalation (smoking), and intravenous injection of amphetamine are increasingly common routes of administration in different populations of users (Klee, 1993; Darke, Cohen, Ross, Hando & Hall, 1994; Hall *et al.*, 1996; Peters, Davies & Richardson, 1997; Charnaud & Griffiths, 1998; Molitor, Ruiz, Flynn, Mikanda, Sun & Anderson, 1999; Weatherburn, Lind & Forsythe, 1999; Kaye & Darke, 2000; Topp, Day & Degenhardt, 2003; Zernig, Giacomuzzi, Riemer, Wakonigg, Sturm & Saria, 2003; Semple, Patterson & Grant, 2004). The popularity of injection and inhalation as routes of amphetamine administration may be related to the production of rapid and intense pharmacologic effects that provide strong positive reinforcement for continued use. Intravenously administered methamphetamine has a mean plasma $t½$ of 11 – 12 hours (Cook *et al.*, 1993; Harris *et al.*, 2003) while the dextroamphetamine $t½$ is around 16 hours (Harris *et al.*, 2003).

In some populations (Perez-Reyes *et al.*, 1991; Cook *et al.*, 1993; Cho & Melega, 2002; Degenhardt & Topp, 2003), particularly in South East Asia (Cheurprakobkit, 2000; National Household Survey Thailand, 2001; Bureau for International Narcotics and Law Enforcement Affairs, 2002; Ahmad, 2003; Humeniuk & Ali, 2004), inhalation of vapour is the preferred route of administration of methamphetamine.

Both inhalation of amphetamine vapour and injection of methamphetamine show similar parameters as found in a laboratory study in healthy volunteers (Cook *et al.*, 1993). In this study, smoked methamphetamine showed bioavailability (90%), markedly higher than by the oral route (67%). The mean plasma *t*½ for smoked methamphetamine (11.1 hours) was similar to that of 12.2 hours for the intravenous administration. In the elimination phase the volume of distribution was 3.24 +/ – 0.36 L/kg for smoked methamphetamine and 3.73 +/ – 0.59 L/kg for the intravenous dose. Therefore, bioavailability of intravenous or inhaled methamphetamine (90%) is substantially higher than after oral dosing (67%) (Cook *et al.*, 1992). A later study using an animal model confirmed and extended these findings, in that the pharmacological effects and the distribution of methamphetamine in brain, plasma and whole body was found to be comparable for inhalation and intravenous routes of administration (Meng, Dukat, Bridgen, Martin & Lichtman, 1999).

1.7.1.3. Intranasal administration

Intranasal administration or snorting of amphetamine has been reported in substantial proportions of amphetamine users. For example, in a sample of 301 Australian amphetamine users, Hall and colleagues found that one quarter had injected or snorted amphetamines in the six months prior to interview (Hall *et al.*, 1996). Methamphetamine is also well absorbed by the intranasal route (Harris *et al.*, 2003) with bioavailability of 79% after intranasal administration. In this study, maximum methamphetamine concentrations occurred at 2.7 hours following intranasal administration. At around 11 hours, the elimination *t*½ was similar to that shown for both intravenous and intranasal routes of administration (Cook *et al.*, 1993; Harris *et al.*, 2003).

1.8. Acute effects of amphetamines: animal models

Studies of the acute effects of amphetamines in animals have concentrated predominantly on the behavioural effects of differing doses of amphetamine.

1.8.1. Locomotor activity and stereotypy

A number of studies have shown that amphetamine treatment produces a striking dose-dependent increase in locomotor activity in animals (see for example Geyer, Russo, Segal & Kuczenski, 1987; McNamara, Davidson & Schenk, 1993; Sills, Greenshaw, Baker & Fletcher, 1999). In addition to increases in locomotor activity, the emergence of stereotypies at moderate to high doses of amphetamines (see for example Kuczenski, Segal & Aizenstein, 1991; Kuczenski & Segal, 1997) has been identified.

Porrino and colleagues demonstrated the different forms of stereotypic behaviour elicited by high and moderate doses of amphetamine. They showed that administration of low doses of intravenously administered amphetamine (0.2 and 0.5 mg/kg) to conscious rats resulted in increased locomotor activity – a moderate dose (1.0 mg/kg) produced locomotion and stereotypic sniffing, while a high dose of amphetamine (5.0 mg/kg), produced stereotypic gnawing and licking (Porrino, Lucignani, Dow-Edwards & Sokoloff, 1984).

Other investigations have also provided detailed assessments of behavioural responses to ascending doses of amphetamine. Antoniou and colleagues identified significant increases in several behaviours in addition to locomotor activity. In this study, amphetamine doses of 0.5, 1.5, 3 and 6 mg/kg were administered to male Wistar rats. Locomotor activity (as measured by photo beam interruptions in a continuous one-hour recording session) was increased significantly relative to saline at all doses, with the greatest response identified following the 3 mg/kg dose. Other behavioural measures such as standing, moving, sniffing, rearing, grooming and freezing showed similar, bell shaped response patterns with reduced frequency at higher doses of amphetamines. In contrast to the other behavioural measures, the frequency of licking (defined as standing, licking the walls of the apparatus) was only significantly greater in comparison to saline following treatment with the highest dose (6 mg/kg) of amphetamine. The authors suggested that the character of behavioural responses to amphetamine may change with increasing dosage – moving from a pattern of increased locomotor activation to a pattern of stereotypy (Antoniou, Kafetzopoulos, Papadopoulou-Daifoti, Hyphantis & Marselos, 1998).

Increased locomotor activity and stereotypic behaviours are thought to be dose dependently associated with the activation of central dopaminergic mechanisms, particularly in the mesolimbic and nigrostriatal regions (see for example Joyce & Koob, 1981; Brauer, Goudie & de Wit, 1997; Kankaanpaa, Meririnne, Lillsunde & Seppala, 1998; Koob, Sanna & Bloom, 1998; Kuczenski & Segal, 1999). However, other systems may also be involved in the mediation of locomotor activity. For example, there is emerging evidence that metabotropic glutamate receptors play a major role in the locomotor stimulant effect of amphetamine, possibly through their functional, either direct or indirect, interactions with D1-like receptors in the nucleus accumbens (David & Abraini, 2003).

1.9. Acute effects of amphetamines: human models

Existing studies of the acute effects of amphetamines in humans have concentrated primarily on the cardiovascular, performance and subjective effects of amphetamine.

1.9.1. Cardiovascular effects

Increased cardiovascular responses following single (Martin, Sloan, Sapira & Jasinski, 1971; Lamb & Henningfield, 1994; Mendelson, Jones, Upton & Jacob, 1995; Johnson, Roache, Bordnick & Ait-Daoud, 1999) and multiple (Angrist *et al.*, 1987; Corwin, Bartlik & Cooper, 1987; Cook *et al.*, 1993; Brauer, Ambre & de Wit, 1996; Makris, Rush, Frederich & Kelly, 2004) doses of experimenter-administered methamphetamine have been demonstrated in a number of studies.

However, varying time courses have been identified for different cardiovascular effects, with heart rate peaking several hours later than blood pressure following dosing (Martin *et al.*, 1971; Angrist *et al.*, 1987; Brauer *et al.*, 1996) (see **Section 1.10 below,** for a more detailed review of the time course of cardiovascular effects). Amphetamine's cardiovascular effects are thought to be mediated by increased release of noradrenaline in both the peripheral and central nervous systems (Rothman *et al.*, 2000).

1.9.2. Performance effects

The stimulant effects of amphetamine have been used to relieve fatigue and enhance performance by a number of groups including sportspeople, truck drivers, shift workers, students and military personnel (Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson & Mac, 1995; Jones & Pichot, 1998; Bowers, 2002; Baker *et al.*, 2004).

In performance terms, amphetamine increases response speed and procedural learning (Kumari, Corr, Mulligan, Cotter, Checkley & Gray, 1997) in normal, healthy subjects. This better performance is thought to be associated with a decrease in impulsive responding and reversal of the effects of fatigue following amphetamine administration (de Wit, Enggasser & Richards, 2002). However, not all studies have identified decreased impulsivity following administration of amphetamine (see for example Fillmore, Kelly & Martin, 2005).

A number of studies have also demonstrated better performance for amphetamine relative to placebo on objective measures of reaction time, logical reasoning and short-term memory (Pigeau *et al.*, 1995; Shappell, Kearns, Valentine, Neri & DeJohn, 1996; Servan-Schreiber, Carter, Bruno & Cohen, 1998). The stimulant effects of amphetamine are of particular interest to occupational groups, such as the defence forces, which require sustained attention over long time periods. In a study of 41 military subjects, Pigeau and colleagues examined the effects of 20 mg of amphetamine compared to placebo on three separate occasions during 64 hours of continuous cognitive work and sleep deprivation. In this study, objective measures of reaction time, logical reasoning and short-term memory clearly showed better performance with amphetamine relative to placebo. Additionally, amphetamine maintained or increased body temperature compared to the natural circadian cycle observed in the placebo group (Pigeau *et al.*, 1995).

1.9.3. Subjective effects

The positive subjective effects of drugs have important implications for their dependence producing potential (de Wit, Uhlenhuth & Johanson, 1986) and are therefore of significant interest to researchers and clinicians. Several studies have demonstrated 'positive' subjective effects following a single dose of experimenter-

administered methamphetamine (Martin *et al.,* 1971; Lamb & Henningfield, 1994; Mendelson *et al.,* 1995). Positive effects have also been identified following multiple amphetamine dosing. For example, in the study by Pigeau and colleagues described in **Section 1.9.2 above**, the effects of three doses (20 mg each) over 64 hours were compared to placebo in 41 sleep deprived military subjects. In this study, amphetamine treated subjects had better mood, less fatigue and less sleepiness in comparison to the placebo treated group (Pigeau *et al.,* 1995).

In a study comparing repeated doses of 10mg amphetamine to placebo in ten normal human volunteers, Johanson and colleagues found that liking scores for amphetamine were consistently higher than for placebo. Other subjective effects in this study were assessed using the Profile of Mood States before administration of amphetamine or placebo, and at 1, 3, and 6 hours after dosing. Compared to placebo, amphetamine produced increased 'anxiety', 'vigour', 'friendliness', 'elation', 'arousal', 'positive mood', and decreased 'fatigue' (Johanson, Kilgore & Uhlenhuth, 1983).

While these studies provide valuable information on subjective responses to amphetamine in humans, recent work by Lott and colleagues has highlighted the importance of individual variability in responses to stimulant drugs. Using a drug challenge approach, the association between DAT1 genotype and subjective responses to amphetamine was examined in a group of normal, healthy adults using a double-blind, crossover design (Lott, Kim, Cook & de Wit, 2005). Subjects received placebo, 10 mg, and 20 mg oral amphetamine in a random fashion, and completed self-report measures on subjective effects. Subjects were genotyped for the DAT1 3'-untranslated region VNTR polymorphism and divided into groups based on genotype: homozygous for nine repeats (9/9, n = 8), heterozygous (9/10, n = 36) and homozygous for 10 repeats (10/10, n = 52). The effects of amphetamine on ratings of 'feel drug', 'anxiety', and 'euphoria' were examined. In 9/10 and 10/10 subjects, amphetamine produced increases in subjective effects such as 'feel drug', 'anxiety' and 'euphoria' as expected. However, in 9/9 subjects, there were no differences between amphetamine and placebo, suggesting that the 9/9 genotype has diminished subjective response to acute amphetamine dosing (Lott *et al.,* 2005).

The positive subjective effects of amphetamine administration are independent of the setting in which dosing occurs. The effect of setting was examined using a within-subjects design in a sample of eight healthy volunteers (Zacny, Bodker & de Wit, 1992). In this study, either oral amphetamine 20mg or placebo was administered in either an inpatient (isolated laboratory room) or an outpatient (normal daily environment) setting. Assessment of subjective drug effects occurred before and after dosing with amphetamine or placebo. In comparison to placebo, amphetamine produced typical stimulant-like subjective effects such as 'elation', 'euphoria', and 'friendliness', but the setting neither quantitatively nor qualitatively altered the drug response (Zacny *et al.*, 1992).

1.10. Relationship of plasma amphetamine concentrations to cardiovascular and subjective measures

Several studies have measured plasma amphetamine concentrations and their relationship to cardiovascular parameters and subjective effects in humans. Angrist and colleagues studied the effects of 0.25 mg/kg of orally administered d-amphetamine in seven normal, healthy subjects (Angrist *et al.*, 1987). Peak amphetamine concentrations of 39.6 ng/ml occurred at three hours post-administration. Blood pressure peaked at one hour when plasma amphetamine concentration was 26 ng/ml and heart rate increased steadily up to the final observation point of five hours at a plasma amphetamine concentration of 39 ng/ml. Maximum subjective changes were noted after two hours with a plasma amphetamine concentration of 39 ng/ml. In the same study, a separate group of eight subjects that received 0.5 mg/kg d-amphetamine orally showed maximum plasma concentration of approximately twice those seen in the 0.25 mg/kg group. In the 0.5 mg/kg group, plasma concentrations peaked at 3 – 4 hours post-administration. Blood pressure and subjective effects were maximal at 2 – 3 hours post-administration and were declining by 4 hours despite stable or rising plasma concentrations (Angrist *et al.*, 1987)

In a later study, Brauer and colleagues examined the effects of 20 mg d-amphetamine in six normal, health males (Brauer *et al.*, 1996). Plasma amphetamine concentrations peaked four hours following administration (40 ng/ml); maximum blood pressure occurred at three hours (plasma concentration of

39 ng/ml) while maximum heart rate occurred at six hours with plasma amphetamine concentrations of 36 ng/ml. Subjective effects were maximal at 1.5 – 2 hours following administration with plasma amphetamine concentrations of 26 – 30 ng/ml.

More recently, Asghar and colleagues studied the effects of single oral doses of d-amphetamine 25mg in 25 normal, healthy males (Asghar *et al.*, 2003). Peak plasma amphetamine concentrations of 40.8 ng/ml occurred at 3.5 hours post-administration. Blood pressure peaked at 1.5 hours post-administration with plasma amphetamine concentrations of 31.5 ng/ml. Maximum subjective effects occurred at 60 – 90 minutes post-administration when plasma amphetamine concentrations were at 19 – 31.5 ng/ml (Asghar *et al.*, 2003). These results indicate that the initial increase in plasma amphetamine levels is reflected in a change in subjective and physiological measurements. However, there is some dissociation between these effects and plasma amphetamine concentrations.

1.11. Effects of amphetamine on appetite

The hypophagic response to amphetamine has been studied extensively in animals, (see for example Hughes, Popi & Wolgin, 1999; Wolgin, 2000; Kuo, Hsu & Cheng, 2001; Wolgin & Hughes, 2001; Hughes & Wolgin, 2002; Wolgin, 2002) and human subjects (Foltin, Kelly & Fischman, 1990; Williamson, Gossop, Powis, Griffiths, Fountain & Strang, 1997; Comer, Hart, Ward, Haney, Foltin & Fischman, 2001; Glazer, 2001; Hart, Ward, Haney, Foltin & Fischman, 2001; Rothman, Blough & Baumann, 2002; Makris *et al.*, 2004). These anorectic properties are exploited in the wide range of amphetamine-like drugs that have been marketed as appetite suppressants (Samanin & Garattini, 1993).

Tolerance to the anorectic effects of amphetamines (within around ten days) has been identified in animals (Caul, Jones & Barrett, 1988; Nencini, 1988; Kuo & Cheng, 2002). Moreover, tolerance to the anorectic effects of amphetamine may be retained for as long as 31 weeks following cessation of dosing (Wolgin & Hughes, 2001). Although the precise mechanism of the anorexic effects of amphetamine is at present unknown, both the beta adrenergic and dopaminergic systems appear to act together in mediating amphetamine anorexia

(Bhakthavatsalam, Kamatchi & Ghosh, 1985), while studies in lesioned animals have indicated that the onset and the rate of completion of tolerance are mediated by the hypothalamic dopaminergic system (Bhakthavatsalam, Kamatchi & Ghosh, 1987). In humans, tolerance to the anorectic effects of amphetamine develops after about three weeks of continuous dosing (Defelice, Chaykin & Cohen, 1973).

1.12. Reinforcing effects of amphetamines

The interoceptive cue properties of amphetamines in animals have been established in a number of drug discrimination studies (see for example Brauer *et al.*, 1997; Munzar, Bauman, Shoaib & Goldberg, 1999; Filip, Nowak, Baran & Przegalinski, 2001). Amphetamine is readily self-administered by animals (Hoffmeister, 1980; McCown & Barrett, 1980; Hoebel, Monaco, Hernandez, Aulisi, Stanley & Lenard, 1983; Sannerud, Brady & Griffiths, 1989), shows strong place preference conditioning (Spyraki, Fibiger & Phillips, 1982; Gilbert & Cooper, 1983; Kruszewska, Romandini & Samanin, 1986; Tzschentke & Schmidt, 1997; Pelloux, Costentin & Duterte-Boucher, 2004) and brain stimulation reward effects (Phillips, Brooke & Fibiger, 1975; Glick, Weaver & Meibach, 1980).

In animals, drug discrimination studies have also facilitated the characterisation of the neurotransmitter – receptor interactions thought to be responsible for mediating the cue properties of amphetamines and to help identify the neuroanatomical structures where these interactions are thought to occur (Kahlig & Galli, 2003; Barrett, Caul & Smith, 2004). The discriminative stimulus effects, which are thought to correspond to euphoria, or the hedonic response to amphetamine in humans, are mediated principally by the mesolimbic dopaminergic projections into the ventral striatum (Munzar *et al.*, 1999; Shi, Pun, Zhang, Jones & Bunney, 2000; Giorgetti, Hotsenpiller, Froestl & Wolf, 2002).

Recent work by Drevets and colleagues has extended this finding to humans. Using positron emission tomography (PET) these authors found that the magnitude of ventral striatal dopamine release correlates positively with the hedonic response to amphetamine (Drevets *et al.*, 2001). However, previous work (Brauer *et al.*, 1997) showing that dopamine receptor antagonists do not block the subjective effects of amphetamine has indicated that the relationship is not a

simple one. In a review of the evidence for the reinforcing effects of amphetamines, Villemagne and colleagues suggested that increased brain dopamine concentrations may be necessary, but not sufficient to produce the subjective effects of amphetamines in humans (Villemagne, Yuan, Wong, Dannals, Hatzidimitriou, Mathews, Ravert, Musachio, McCann & Ricaurte, 1998).

A number of studies have identified the reinforcing effects of both amphetamine and methamphetamine in humans (Johanson *et al.*, 1983; Foltin & Fischman, 1991; Gable, 1993; Rush, Kollins & Pazzaglia, 1998; Johnson *et al.*, 1999; Schuckit, Daeppen, Danko, Tripp, Smith, Hesselbrock & Bucholz, 1999; Hart *et al.*, 2001). Dependence potential studies among healthy volunteers indicate that amphetamine is preferred to placebo, producing changes in mood including increased anxiety, vigour, friendliness, elation, arousal, positive mood, and decreased fatigue (Johanson *et al.*, 1983). Similarly, methamphetamine produces increases in positive subjective measures of both stimulation and mood (Johnson *et al.*, 1999). However, in humans, the reinforcing effects of amphetamine depend to some degree on the route of administration. As noted in **Section 1.7.1.2 above**, because of the rapid and intense drug effects experienced in comparison to other nonparenteral routes of administration such as oral administration, for many amphetamine users, intravenous injection or inhalation of amphetamine vapour are the preferred routes of administration (Darke *et al.*, 1994; Peters *et al.*, 1997; Matsumoto, Kamijo, Miyakawa, Endo, Yabana, Kishimoto, Okudaira, Iseki, Sakai & Kosaka, 2002).

As Shoblock and colleagues have noted, there is a widely held view that methamphetamine is a more potent drug with stronger central stimulant effects in comparison to amphetamine. Additionally, substance users are said to prefer methamphetamine to amphetamine and that consequentially, methamphetamine possesses a greater potential for dependence. However, no abuse liability studies comparing amphetamine to methamphetamine have been carried out to date and evidence is lacking for this widely held view (Shoblock, Sullivan, Maisonneuve & Glick, 2003). For example, several lines of evidence show that amphetamine and methamphetamine are self-administered at comparable rates in animals (Balster & Schuster, 1973; Oberlender & Nichols, 1988; Bondareva, Young & Glennon, 2002;

McMillan, Hardwick, Li & Owens, 2002) while humans show a preference for similar doses of amphetamine and methamphetamine (Martin *et al.*, 1971). Further, evidence from drug discrimination studies show that neither humans nor animals discriminate between equal doses of methamphetamine and amphetamine (Huang & Ho, 1974; Kuhn, Appel & Greenberg, 1974; Lamb & Henningfield, 1994; Peltier, Li, Lytle, Taylor & Emmett-Oglesby, 1996). Only one study that directly compared the acute locomotor activating effects of equivalent doses of methamphetamine and amphetamine was found in the literature. Using female rats, this study found no evidence that methamphetamine was a greater central psychomotor stimulant in comparison to amphetamine (Shoblock *et al.*, 2003).

1.13. Tolerance and sensitisation

Tolerance to the effects of amphetamines following repeated use over time is commonly reported by dependent amphetamine users and is a criterion for a diagnosis of dependence (DSM-IV-TR, 2000). For example, almost all (95%) of a large cohort of current amphetamine users reported tolerance to the effects of amphetamine during their lifetime (Topp & Darke, 1997). However, as noted in previous sections, amphetamines have a range of effects and tolerance to some of the drug effects develops at different times. Moreover, tolerance studies have produced mixed results.

For example, acute tolerance to the subjective but not cardiovascular effects of d-amphetamine in normal, healthy males has been reported (Brauer *et al.*, 1996). In this study, plasma drug levels peaked at four hours following single oral doses of 20 mg of d-amphetamine and remained at detectable concentrations for 24 hours. Subjective ratings, including 'feel drug' and 'feel high' peaked at 1½ – 2 hours and returned to baseline levels by three to four hours despite substantial plasma concentrations. Systolic blood pressure rose during the first hour, remaining elevated for the 24 hour monitoring period. In contrast, heart rate did not begin to increase until around three hours then remained elevated at 24 hours (Brauer *et al.*, 1996).

Another study found no tolerance or change in the sensitivity of behavioural responses after nine daily oral doses of 10mg of d-amphetamine in normal human volunteers (Johanson *et al.*, 1983). Similar results were found after 13 consecutive daily administrations of 10mg of methamphetamine as a slow-release preparation in another laboratory study, this time in male amphetamine users. There was no change in subjective ratings of 'high' over the study time period, although tolerance to the cardiovascular effects was identified, specifically a significant decrease in heart-rate acceleration in response to methamphetamine challenge at the end of the study period (Perez-Reyes *et al.*, 1991). It should be noted that both of these studies used a low dose of oral amphetamine (10mg).

Higher doses were used in a 15 day residential study that sought to replicate the binge pattern use commonly seen in amphetamine users (Comer *et al.*, 2001). In this study, seven normal, healthy volunteers completed subjective-effects questionnaires and psychomotor performance tasks in multiple testing sessions. Oral methamphetamine (5, 10 mg twice a day) was administered on days 4 – 6 and 10 – 12, and placebo administered on all other days. Only two positive subjective ratings – 'feel a good drug' effect and 'feel high' – were significantly elevated in comparison to placebo – and only on the first day of methamphetamine treatment. Conversely, several negative ratings, including 'bad drug effect' 'dizziness' and 'flu-like symptoms' were elevated on the third day of methamphetamine treatment. In this study, tolerance to the positive subjective effects of orally administered methamphetamine occurred rapidly while sensitisation to the negative subjective effects increased after repeated administration (Comer *et al.*, 2001). The finding that relatively few positive subjective effects were increased in this study is in contrast to those reported by current amphetamine users (Martin *et al.*, 1971) and may have been a function of drug expectancies or the setting of drug use.

In contrast to tolerance, whereby increasing doses are required to achieve the same drug effects, sensitisation is a progressively greater and enduring behavioural response that occurs following repeated drug administration (Strakowski, Sax, Rosenberg, DelBello & Adler, 2001). Importantly, behavioural sensitisation is thought to contribute to the dependence potential and harms

associated with amphetamine and other substance use (Robinson & Becker, 1986; Robinson & Berridge, 1993).

While there is a large body of evidence for behavioural sensitisation to amphetamines in animals (see for example Kittner, Krugel & Illes, 2001; Kuczenski & Segal, 2001; Anagnostaras, Schallert & Robinson, 2002; Fowler, Birkestrand, Chen, Vorontsova & Zarcone, 2003), few human studies have been conducted and those studies which have examined this phenomenon have produced mixed findings. Behavioural sensitisation to oral doses of d-amphetamine (0.25mg/kg) at two 48 hour intervals were identified in a placebo-controlled study in normal healthy subjects (Strakowski, Sax, Setters & Keck, 1996). Following the second dose, subjects who received amphetamine showed significantly greater (observer-rated) eye blink rates and reported increased energy, mood and talkativeness in comparison to the first dose of amphetamine and both doses of placebo. A later study using a similar design but extending the testing period to three 48 hour intervals found a progressive increase in eye blink rate, motor activity, mood and talkativeness (Sax & Strakowski, 1998).

In a later study utilising a parallel groups design and subjective measures, both tolerance and sensitisation were demonstrated in a laboratory study with normal healthy volunteers, when tolerance to subjective effects (drug liking) and sensitisation to feelings of 'vigour' and 'euphoria' were identified following oral administration of amphetamine (Strakowski *et al.*, 2001). Other studies have failed to identify behavioural sensitisation in healthy volunteers administered two doses of oral d-amphetamine (20mg) at 48 hour intervals alternating with placebo (Wachtel & de Wit, 1999).

In animals, exposure to amphetamine can produce a rapid sensitisation of the stereotypy response to amphetamines that is thought to be mediated by both D_1 and D_2 dopamine receptor activity (Kuczenski & Segal, 1999, 1999).

It may be as has been suggested, that different subjective effects of amphetamine are mediated though separate neurobehavioural mechanisms, such that some effects exhibit sensitization with repeated dosing while others develop tolerance.

1.14. Amphetamine dependence

Until relatively recently amphetamine use was not thought to be associated with significant dependence and/or withdrawal symptoms on cessation (Nir, 1980; Morgan, 1981). Where withdrawal symptoms did occur, they were thought to be mild and transient (Jones & Jones, 1977) even following high dose use (Smith, 1969). The absence of a documented withdrawal syndrome was inconsistent however with the finding by several authors (Johanson *et al.*, 1983; Foltin & Fischman, 1991; Gable, 1993) that amphetamine had a relatively high abuse potential.

Amphetamine dependence was first measured by Gossop and colleagues in English and Australian samples of heroin, cocaine and amphetamine users (Gossop, Darke, Griffiths, Powis, Hall & Strang, 1995). This collaborative study resulted in the development of the Severity of Dependence Scale (SDS) a valid and brief scale that is useful in the measurement of heroin, cocaine, benzodiazepine and amphetamine dependence. Further evidence of a dependence syndrome associated with amphetamine use was provided by a series of studies conducted in the 1990s (Churchill, Burgess, Pead & Gill, 1993; Lintzeris, Holgate & Dunlop, 1996; Topp & Darke, 1997; Topp & Mattick, 1997; Cantwell & McBride, 1998). In the Churchill *et al.,* study, two existing dependence questionnaires, the Severity of Opiate Dependence Questionnaire (Sutherland, Edwards, Taylor, Phillips, Gossop & Brady, 1986) and the Alcohol Dependence Questionnaire (Stockwell, Murphy & Hodgson, 1983) were modified to produce a questionnaire measuring dependence on amphetamine – the Severity of Amphetamine Dependence Questionnaire (SAmDQ) (Churchill *et al.*, 1993).

1.15. Amphetamine withdrawal

Although the neurobiology of amphetamine withdrawal is not yet clearly understood, as amphetamine interacts with noradrenergic, dopaminergic and serotonergic neuronal pathways, increasing synaptic neurotransmitter concentrations, it is possible that symptoms of withdrawal are indicative of a state of relative functional depletion of these neurotransmitters in the brain when amphetamine use is ceased. A model of stimulant (including amphetamine)

withdrawal based on the dual deficit model has been proposed by Rothman and colleagues (Rothman, Partilla, Dersch, Carroll, Rice & Baumann, 2000).

According to this model, the anhedonia and psychomotor retardation observed during stimulant withdrawal is a function of dopamine depletion, while the depressed mood, obsessional thoughts and lack of impulse control is a function of 5-HT depletion (Rothman *et al.*, 2000). While this model is yet to be tested in human subjects, some studies have identified low concentrations of dopamine during withdrawal from other psychostimulants such as cocaine (McDougle, Price, Palumbo, Kosten, Heninger & Kleber, 1992; Bowers, Malison, Seibyl & Kosten, 1998).

Some features of amphetamine withdrawal have been studied extensively in animals i.e. sexual behaviour (Barr, Fiorino & Phillips, 1999), impulsivity (Peterson, Wolf & White, 2003), fear (Pezze, Feldon & Murphy, 2002) and depression (Schreiber, Bell, Conely, Kufner, Palet & Wright, 1976; Cassens, Actor, Kling & Schildkraut, 1981; Kokkinidis, Zacharko & Anisman, 1986; Paulson, Camp & Robinson, 1991; Paterson, Myers & Markou, 2000; Barr, Markou & Phillips, 2002; Cryan, Hoyer & Markou, 2003; Russig, Pezze, Nanz-Bahr, Pryce, Feldon & Murphy, 2003). Importantly, animal models of amphetamine withdrawal have identified synaptic deficits of both dopamine and serotonin (Imperato, Obinu, Carta, Mascia, Casu & Gessa, 1996; Weiss, Imperato, Casu, Mascia & Gessa, 1997) and have provided evidence that behavioural depression was associated with a transient decrease in hypothalamic concentrations of noradrenaline (Paulson *et al.*, 1991).

However, reductions in extracellular dopamine concentrations are common to the withdrawal syndrome from a range of psychoactive substances. For example, rats withdrawing from chronic ethanol, morphine, cocaine and amphetamine showed substantial reductions in extracellular dopamine concentrations in the ventral striatum as measured by microdialysis (Rossetti, Hmaidan & Gessa, 1992).

Although the existence of an amphetamine dependence syndrome has been recognised (Churchill *et al.*, 1993; Topp & Darke, 1997; Topp & Mattick, 1997, 1997), there is a paucity of evidence-based information on the nature and time

course of the amphetamine withdrawal syndrome in humans. The DSM-IV has provided a set of clinically derived criteria for characterising amphetamine withdrawal (DSM-IV-TR, 2000). According to the DSM-IV, withdrawal is defined by 'the presence of a characteristic withdrawal syndrome that develops within a few hours to several days after cessation of (or reduction in) heavy and prolonged amphetamine use (Criteria A and B) '. The amphetamine withdrawal syndrome is characterised by the presence of dysphoria and two or more physiological changes (see 1 – 5 below)

A.   Cessation of (or reduction in) amphetamine (or a related substance) use that has been heavy and prolonged.

B.   Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after Criterion A:

Physiological changes

1.   Fatigue

2.   Vivid, unpleasant dreams

3.   Insomnia or hypersomnia

4.   Increased appetite

5.   Psychomotor retardation or agitation

C.   The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D.   The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

The DSM-IV also refers to the occurrence of a 'crash' characterised by intense and unpleasant feelings of lassitude and depression that generally require several days of rest. Additionally, the anorectic effect of amphetamines, which may cause weight loss during periods of amphetamine use is noted, as is the converse increase in appetite with subsequent weight gain during withdrawal. The DSM-IV

also notes that symptoms of depression (including suicidal ideation) may persist for up to several weeks (DSM-IV-TR, 2000).

1.15.1. Incidence of amphetamine withdrawal symptoms

Large studies conducted in the United States and in Australia have identified a high incidence of self-reported withdrawal symptoms in amphetamine users. For example, in a study of regular (at least monthly) amphetamine users (n = 331) surveyed in Sydney, Australia, almost all (97%) had experienced withdrawal symptoms on cessation of amphetamine use, while for 78% of participants, withdrawal symptoms were relieved on reinstatement of amphetamine use (Topp & Darke, 1997). A later study of 647 amphetamine dependent individuals found that 87% reported having experienced withdrawal symptoms on cessation of use (Schuckit *et al.*, 1999).

1.15.2. Nature of amphetamine withdrawal symptoms

While these studies have shown that withdrawal symptoms are common among amphetamine users and the DSM-IV provides useful information on the diagnostic criteria for amphetamine withdrawal, there are few published studies on the specific symptoms reported by amphetamine users. In those reports that have been published, the types of symptoms reported vary. For example, in one of the earliest reports of amphetamine withdrawal symptoms in humans, feelings of fatigue, sleepiness and depression were most commonly reported (Monroe & Drell, 1947) while in interviews with 74 methamphetamine users by Hawks and colleagues in the United Kingdom, aggression, agitation and anxiety were the symptoms most frequently associated with 'coming down' (Hawks, Mitcheson, Ogborne & Edwards, 1969). Later, Angrist and Sudilovsky (1978) noted the presence of depression, hyperphagia, hypersomnia and psychomotor retardation in patients withdrawing from amphetamines (Angrist & Sudilovsky, 1978).

Two retrospective studies of amphetamine users identified a wide range of withdrawal symptoms (Churchill *et al.*, 1993; Topp & Mattick, 1997). Many of these symptoms were consistent with those experienced in opioid withdrawal. This finding may have been a function of the questionnaire used, the Severity of Amphetamine Dependence Questionnaire (SAmDQ), which is based, in part, on

an opiate dependence questionnaire, the Severity of Opiate Dependence Questionnaire (SODQ), or it may reflect a common neurobiological mechanism of dependence across difference drug categories as suggested by other authors (Wise & Bozarth, 1987). Another retrospective study of 50 dependent amphetamine users in the UK, by Cantwell and McBride found that the majority (86%) had experienced significant withdrawal symptoms on cessation of use, principally irritability, aches and pains and depression (Cantwell & McBride, 1998). Importantly, subjects in this study reported that amphetamine withdrawal symptoms persisted for between five days and three weeks.

A later study using the Beck Depression Inventory (Beck, Ward, Mendelson, Mock & Erbaugh, 1968) in a non treatment seeking sample of amphetamine users found a significant reduction in depression over the first three days of abstinence. Early abstinence in this sample was characterised principally by symptoms of anhedonia, irritability and poor concentration (Newton, Kalechstein, Duran, Vansluis & Ling 2004).

1.15.3. Depression

Dysphoria, an essential criterion for the diagnosis of amphetamine withdrawal (DSM-IV-TR, 2000), is substantially higher in stimulant-dependent individuals in comparison to the general community (Kosten, Markou & Koob, 1998). Depression is commonly identified in treatment samples (Watson, Hartmann & Schildkraut, 1972; Cantwell & McBride, 1998; Srisurapanont, Jarusuraisin & Jittiwutikarn, 1999, 1999; Domier, Simon, Rawson, Huber & Ling, 2000; Srisurapanont *et al.*, 2003; Jenner & Saunders, 2004; Zweben, Cohen, Christian, Galloway, Salinardi, Parent & Iguchi, 2004) and community samples (London, Simon, Berman, Mandelkern, Lichtman, Bramen, Shinn, Miotto, Learn, Dong, Matochik, Kurian, Newton, Woods, Rawson & Ling, 2004; Newton *et al.*, 2004) of amphetamine users. Moreover, in some methamphetamine users, dysphoric symptoms may persist for several years after treatment even where substance use is reduced (Rawson, Huber, Brethen, Obert, Gulati, Shoptaw & Ling, 2002).

While amphetamine withdrawal has been postulated as a possible animal model for endogenous depression (Barr *et al.*, 2002; Barr, Zis & Phillips, 2002) as Angrist

and Sudilovsky have noted there are important qualitative differences in symptom presentation between the two conditions. For example, hyperphagia and hypersomnia are prominent features of amphetamine withdrawal symptomatology while hypophagia and hyposomnia are more commonly seen in endogenous depression.

1.15.4. Sleep patterns

The stimulant properties of amphetamine can relieve fatigue and reduce the need for sleep (Comer *et al.*, 2001; Chapotot, Pigeau, Canini, Bourdon & Buguet, 2003). Indeed, the extended waking hours and stimulation are regarded as desirable properties of the drug and can lead to instrumental use in people seeking to alleviate fatigue in a range of situations e.g., long distance truck drivers, chefs, shift workers and students (Baker *et al.*, 2004). The stimulant properties of amphetamines are reflected in studies of current users. For example, in one study of 74 polydrug users (principally methamphetamine injectors) in the UK only 22% had slept for more than two hours in any 24 hour period during the week prior to interview (Hawks *et al.*, 1969).

Sleep disturbance during withdrawal from regular amphetamine use has also been reported (Monroe & Drell, 1947; Angrist & Sudilovsky, 1978; Gossop, Bradley & Brewis, 1982). Importantly, Angrist and Sudilovsky (1978) noted that even where patients had sufficient sleep, they still experienced several days of fatigue in the early phase of abstinence. In an early series of case reports that examined withdrawal symptoms in stimulant (mostly amphetamine) users, Oswald and Thacore reported disturbances of sleep architecture, principally decreased latency to REM sleep and increased total REM sleep on cessation of regular stimulant use. Importantly, sleep patterns in these patients took three to eight weeks to return to normal (Oswald & Thacore, 1963).

There are also clinical reports of an initial 'crash' period of around three days following the cessation of amphetamine use. The crash phase, during which the individual may sleep for much of the time, may be followed by a prolonged period of insomnia (King & Ellinwood, 1997). Gossop and colleagues investigated sleep duration in hospitalised amphetamine users (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 study period of 20 days. While hours of sleep for amphetamine users were greater than or similar to controls on nights 1 – 5, amphetamine users slept less than controls on nights 6-20 when the study ended. Night time sleep among the amphetamine users peaked at just over eight hours on the second night and fell thereafter to a low of around five hours on the ninth night since admission. By the 20th night, amphetamine users in this study were sleeping around six hours per night. These data do not provide support for clinical reports of a 'crash' following cessation of amphetamine use, rather an initial period of 'normal' sleep followed by a prolonged period (at least 15 days) of relative insomnia. Although this study yielded valuable information on the sleep patterns of amphetamine users in the initial three weeks of abstinence, no data on the intensity or frequency of amphetamine use was reported and no other withdrawal symptoms were measured.

1.15.5. Craving

Clinical reports indicate that craving for amphetamines is a substantial feature of the withdrawal syndrome promoting continued use in dependent users. However, one of the difficulties in any attempt to assess craving related variables is the problem of defining craving and urges to use psychoactive substances in operational terms and, importantly, to associate these cognitive states with subsequent drug use (Sayette, Shiffman, Tiffany, Niaura, Martin & Shadel, 2000). Tiffany has conducted an extensive review of studies that associated reports of craving with consumption measures of drugs and revealed only an overall modest correlation of 0.4 (Tiffany, 1990).

However, Hartz and colleagues have shown that when measured prospectively, craving emerges as a salient predictive factor in continued amphetamine use for patients in treatment for amphetamine dependence (Hartz, Frederick-Osborne & Galloway, 2001). In a prospective, repeated-measures, within-subject analysis, this study found that craving intensity (measured on a visual analogue scale) significantly predicted amphetamine use in the week immediately following each craving report even when controlling for other variables (i.e., pharmacological intervention, and amphetamine use during the prior week).

1.15.6. Time course and severity of amphetamine withdrawal symptoms

Amphetamine withdrawal has been reported to peak around 2 – 4 days after cessation of use (Lago & Kosten, 1994). However, only one study has been conducted that systematically examined a range of amphetamine withdrawal symptoms over time. In a randomised, placebo-controlled, double blind study, Srisurapanont and colleagues examined the benefits of amineptine in treating amphetamine withdrawal in an inpatient sample. Amphetamine withdrawal symptoms were measured at three time points during treatment using the Amphetamine Withdrawal Questionnaire (AWQ) (Srisurapanont *et al.*, 1999). In comparison to controls, the amineptine group showed significant reductions in three symptoms, fatigue, increased appetite and increased sleep at the end of the first and second week of treatment. However, amineptine has since been withdrawn from sale due to reports of abuse (Srisurapanont *et al.*, 1999). While this trial provided valuable information on amphetamine withdrawal treatment, symptoms in this study were measured at only three time points, each one week apart. Additionally, assessment time points were determined by the time of admission for inpatient treatment rather than being anchored to the time of last amphetamine use.

Therefore, while a number of studies have provided important information on the nature of the dependence syndrome and the incidence of withdrawal symptoms, little information on the time course and severity of specific withdrawal symptoms has been provided. Therefore, despite these studies, there is a substantial knowledge gap regarding the nature, time course and severity of specific withdrawal symptoms (Baker *et al.*, 2004). The lack of systematic measurement represents an important gap in the literature on amphetamine withdrawal and dependence.

1.16. Treatment of amphetamine dependence and withdrawal

In animals, decreased motivation to work for a natural reward is one of the signs of amphetamine withdrawal and is thought to be a function of hypofunction of the mesolimbic dopamine system. It is possible that medications targeting the presumed depletion of catecholamines may potentially alleviate one or more of the

symptoms of amphetamine withdrawal and preclinical studies are underway. In a recent study, amphetamine trained rats showed reduced responding for a sweet solution in a progressive ratio schedule during withdrawal from repeated amphetamine administration (Orsini, Koob & Pulvirenti, 2001). Systemic treatment with terguride (0.2 and 0.4 mg/kg, i.p.), a dopamine partial agonist administered twice daily during the first four days of amphetamine withdrawal reversed the decrease in responding for the sweet solution. This finding suggests that due to their agonist actions under these conditions, partial dopamine agonists may have therapeutic potential in the treatment of amphetamine withdrawal (Orsini *et al.*, 2001). While animal studies such as these have been encouraging, studies of direct and indirect dopamine agonists in human models of substance dependence have been disappointing (for review see Kosten, George & Kosten, 2002).

1.16.1. Neurotransmitter blocking drugs

There is also interest in medications that address amphetamine dependence by potentially blocking the reinforcing effects of amphetamines. As noted in **Section 1.12 above**, the discriminative stimulus effects, which are thought to correspond to euphoria, or the hedonic response to amphetamine in humans, are mediated principally by its dopaminergic effects (Munzar *et al.*, 1999; Shi *et al.*, 2000; Drevets *et al.*, 2001; Giorgetti *et al.*, 2002). GBR12909, a high affinity dopamine uptake inhibitor, has been shown to attenuate cocaine and amphetamine-induced increases in mesolimbic dopamine in rodent microdialysis studies (Baumann, Char, De Costa, Rice & Rothman, 1994). GBR12909 also markedly inhibited amphetamine-induced striatal dopamine release in a baboon model (Villemagne, Wong, Yokoi, Stephane, Rice, Matecka, Clough, Dannals & Rothman, 1999). There is also evidence that a long-acting preparation of GBR12909 is similarly effective. Using in vivo microdialysis, Baumann and colleagues showed that a long-acting oil-soluble preparation of GBR12909 (GBR-decanoate) elevated basal synaptic dopamine concentrations and blocked methamphetamine-evoked dopamine release, without affecting dopamine receptor function. Moreover, the decreased dopamine transporter binding in the rat nucleus accumbens was sustained for at least two weeks (Baumann, Phillips, Ayestas, Ali, Rice & Rothman, 2002).

Lobeline, classified as both an agonist and an antagonist at nicotinic receptors, appears to inhibit dopamine uptake and promote dopamine release from the storage vesicles within the presynaptic terminal, by interacting with the tetrabenazine-binding site on the vesicular monoamine transporter (VMAT2). Lobeline inhibited amphetamine-induced release of dopamine in vitro, and amphetamine-induced hyperactivity, drug discrimination, and self-administration in animal models (Dwoskin & Crooks, 2002). The identification and development of lobeline and lobeline analogs with targeted selectivity at VMAT2 may provide an alternative treatment approach for highly motivated clients analogous to the use of the opioid antagonist naltrexone in opioid dependence (Gowing, Proudfoot, Henry-Edwards & Teesson, 2001).

While the increase in amphetamine use (Topp, Darke, Bruno, Fry, Hargreaves, Humeniuk, McAllister, O'Reilly & Williams, 2001) and dependence has resulted in greater demands on treatment services (Jenner & McKetin, 2004), current approaches to treatment of amphetamine dependence are limited. This gap in the literature has been noted by a number of recent reports which have drawn attention to the limited range of available treatments (Cretzmeyer, Sarrazin, Huber & Block, 2003; Srisurapanont *et al.*, 2003; Baker *et al.*, 2004; Shearer & Gowing, 2004) particularly in comparison to other drugs of dependence.

1.16.2. Psychological interventions for amphetamine dependence

In the absence of an established pharmacotherapy for amphetamine dependence, psychotherapeutic approaches, delivered in group or individual format, constitute the primary treatment modality currently available for amphetamine users seeking treatment (Stitzer & Walsh, 1997; Baker, Boggs & Lewin, 2001; Gowing *et al.*, 2001; Baker, Kay-Lambkin, Lee, Claire & Jenner, 2003; Baker & Lee, 2003; Baker *et al.*, 2004; Rawson, Marinelli-Casey, Anglin, Dickow, Frazier, Gallagher, Galloway, Herrell, Huber, McCann, Obert, Pennell, Reiber, Vandersloot & Zweben, 2004; Baker, Lee, Claire, Lewin, Grant, Pohlman, Saunders, Kay-Lambkin, Constable, Jenner & Carr, 2005).

However, as for pharmacotherapeutic approaches, only a small number of studies evaluating psychological interventions in amphetamine dependence have been

conducted to date. Two reviews of controlled trials of psychosocial interventions among psychostimulant users (Baker & Lee, 2003; Baker *et al.*, 2004) concluded that motivational interviewing and cognitive behavioural therapy may be promising approaches to amphetamine dependence treatment. However, only two randomised controlled trials of cognitive behaviour therapy for amphetamine dependence have been conducted to date (Baker *et al.*, 2001; Baker *et al.*, 2005) In a pilot study, regular amphetamine users were randomised to one of three conditions. A two session intervention consisting of a motivational interview and discussion of skills (*n* = 16) or a four session intervention consisting of a motivational interview and skills training in avoidance of high-risk situations, coping with craving and relapse prevention (*n* = 16). The control group (*n* = 32) received a self-help booklet. In this study, amphetamine users who had received three or four intervention sessions were more likely to report amphetamine abstinence at six months follow-up in comparison to controls. These findings were replicated in a later study using a similar design and a larger sample of 214 regular amphetamine users (Baker *et al.*, 2005),

The Matrix model, a manualised 16 week intensive outpatient intervention for psychostimulant dependence has shown promise in open trials with methamphetamine users (Huber, Ling, Shoptaw, Gulati, Brethen & Rawson, 1997; Rawson, Huber, Brethen, Obert, Gulati, Shoptaw & Ling, 2000). The Matrix model utilises an approach based on cognitive behavioural therapy, stimulant education, family education, 12-step programs and positive reinforcement for behaviour change and treatment compliance. The Matrix model was recently evaluated in comparison to treatment as usual in a multi site, randomised clinical trial involving 978 treatment-seeking methamphetamine dependent individuals. Treatment retention, clinic attendance, incidence and duration of methamphetamine abstinence (confirmed by urinalysis), was significantly greater in those individuals assigned to receive treatment using the Matrix model. However, while gains in terms of improvements in substance use and psychosocial functioning remained, group differences did not persist at six months follow-up (Rawson *et al.*, 2004). Therefore, although the number of randomised controlled trials of psychological interventions for amphetamine dependence remains small, the available evidence

to date suggests that long-term intensive psychotherapy does not offer any advantage over brief interventions for amphetamine dependence treatment.

1.16.3. Pharmacotherapies for amphetamine dependence and withdrawal

Few pharmacotherapies have been investigated by means of randomised controlled trials for the treatment of amphetamine withdrawal and dependence. A review of the literature identified only four randomised controlled trials of pharmacotherapies for amphetamine dependence. Those drugs that have been tested include the tricyclic antidepressants desipramine (Tennant, Tarver, Pumphrey & Seecof, 1986) and imipramine (Galloway, Newmeyer, Knapp, Stalcup & Smith, 1996); the dopamine agonist antidepressant amineptine (Srisurapanont *et al.*, 1999); the selective serotonin reuptake inhibitor, fluoxetine (Batki, Moon, Bradley, Hersh, Smolar, Mengis, Delucchi, Sexe, Bennett, Lefkowitz, Chu, Morello, Jacob & Jones, 1999) and the calcium channel blocker, amlodipine (Batki, Moon, Delucchi, Hersh, Bradley, Aguillon-Doms, Mendelson, Jones, Panganiban, Everhart, Mengis, Smolar, Helmke & Jacob, 2001). These randomised controlled trials are reviewed below.

The tricyclic antidepressant desipramine was administered to two pairs of amphetamine-dependent subjects under double-blind conditions. The two subjects who received desipramine remained in treatment longer and submitted more amphetamine-negative urine samples than did subjects who received placebo (Tennant *et al.*, 1986). Although this study was conducted under double-blind conditions, the low number of subjects makes generalisation of the results problematic.

Another tricyclic antidepressant, imipramine was found to have limited success (Galloway *et al.*, 1996). In this study, 32 methamphetamine dependent subjects were randomly assigned to receive either 10 mg (control group) or 150 mg per day of imipramine for 180 days. Subjects who received 150 mg of imipramine were retained significantly longer in treatment in comparison to the 10 mg group (median days: 33.0 compared to 10.5). However, there were no significant differences in depression, methamphetamine craving or in the percentage of

methamphetamine positive urine samples between the two groups (Galloway *et al.*, 1996).

Srisurapanont and colleagues examined the benefits of amineptine in treating amphetamine withdrawal (Srisurapanont *et al.*, 1999). In this study, withdrawal symptoms were measured by the Amphetamine Withdrawal Questionnaire (AWQ) (Srisurapanont *et al.*, 1999). Significant differences were found on one of the AWQ subscales, the reversed vegetative subscale that comprised items assessing fatigue, increased appetite and increased sleep. In comparison to controls, the amineptine group showed significantly less severe withdrawal symptoms on the reversed vegetative subscale at the end of weeks one and two. While these results were encouraging, amineptine has since been withdrawn from sale due to reports of abuse.

In a controlled trial of fluoxetine in the treatment of amphetamine dependence, Batki and colleagues reported the preliminary results of a trial to test the efficacy of fluoxetine in the outpatient treatment of amphetamine dependence (Batki *et al.*, 1999). This study was designed as an eight week randomised controlled parallel group study with a one week single-blind placebo lead-in, followed by seven weeks of double-blind fluoxetine 40 mg or placebo per day. While amphetamine use in both groups declined over the study period, craving was significantly lower in the fluoxetine treated group.

Batki and colleagues evaluated the efficacy of the calcium channel blocker amlodipine in an eight week, double-blind, randomised, placebo-controlled, parallel groups trial of amlodipine 5 mg (n = 25) or 10 mg (n = 26) per day compared to placebo (n = 26) in methamphetamine dependent outpatients (Batki *et al.*, 2001). Neither dose of amlodipine was effective – there were no significant group differences in the amount or cost of methamphetamine used, depression or methamphetamine craving.

Therefore, of the four drugs evaluated for the treatment of amphetamine dependence and withdrawal, the antidepressants desipramine, imipramine and fluoxetine showed limited promise. While the dopamine agonist antidepressant amineptine was effective for some symptoms it is no longer available for use.

1.16.4. Substitution treatment for amphetamine dependence

Maintenance agonist treatment approaches have proven effective in the treatment of opioid dependence, with methadone (Ward, Mattick & Hall, 1992) and more recently buprenorphine (Gowing, Ali & White, 2002) having the greatest empirical support. While maintenance treatment of amphetamine dependence has been shown to attract and retain dependent users in treatment as well as improving treatment outcomes (Klee, 1992; Hando, Howard & Zibert, 1997), there is mixed support for long-term maintenance treatments (Mattick & Darke, 1995; White, 2000), and concerns regarding potential toxicity (Sato, 1986).

In the UK, substitution programs for amphetamine dependence have been available for several years. A 1995 national survey of community pharmacies prescribing amphetamines to drug users estimated that, at any one time, 900 – 1000 patients were prescribed amphetamine for the treatment of addiction in England and Wales (Strang & Sheridan, 1997). The majority of prescriptions were for dexamphetamine tablets (73%), 24% were for oral liquid, and 3% were for injectable amphetamines.

Several studies have reported positive outcomes of these programs. These include reductions in the illicit use of amphetamines, as well as reductions in injecting (Charnaud & Griffiths, 1998; Fleming & Roberts, 1994; Klee et al., 2001; McBride et al., 1997; Pates et al., 1996; Shearer et al., 2001; White, 2000). Studies have consistently reported decreases in criminal activity and needle sharing (Fleming & Roberts, 1994; McBride et al., 1997; Pates et al., 1996) and improvements in general health and social functioning (Charnaud & Griffiths, 1998; Fleming & Roberts, 1994; Klee et al., 2001; McBride et al., 1997; Pates et al., 1996; White, 2000). In addition, the availability of maintenance treatment increased the number of users presenting to the service as well as increasing retention rates in treatment (Fleming & Roberts, 1994; McBride et al., 1997).

As well as positive clinical outcomes, studies have found that the incidence of side effects associated with substitution therapy for amphetamine dependence is low (Carnwath et al., 2002; Charnaud & Griffiths, 1998; Shearer et al., 2001). One study reported that three subjects (4.7%) had an episode of psychosis, but these

were related to factors other than the prescription of dexamphetamine (McBride, Sullivan, Blewett & Morgan, 1997). Similarly, White (2000) reported that only five patients (3.4%) recorded psychotic episodes, and in all cases they had a previous history of psychosis and continued to use illicit amphetamines during the treatment period. No patients experienced a first psychotic episode while using dexamphetamine, even after one year of treatment.

However, with the exception of the Australian study (Shearer, Wodak, Mattick, Van Beek, Lewis, Hall & Dolan, 2001) these outcome studies have been uncontrolled and retrospective (Bradbeer et al., 1998) and large randomised controlled trials are needed to provide empirical evidence of the effectiveness of substitution treatment for amphetamine dependence.

1.17. Harms associated with amphetamine use

The increased use of amphetamines and the harms associated with that use is reflected in the increasing numbers of people seeking treatment for amphetamine-related problems (Jenner & McKetin, 2004; McKetin & McLaren, 2004). The major harms associated with the use of amphetamines include the transmission of blood borne viruses, criminal behaviour, aggression and violence, and mental health problems including psychosis and depression. These harms are discussed below.

1.17.1. Transmission of blood borne viruses

Intravenous injection, especially when equipment is shared with others is a route of administration that carries a high risk of transmitting blood borne viruses. Injection is a common route of administration for psychoactive substances in Australia (Darke *et al.*, 1994; Kaye & Darke, 2000). For example, Darke and colleagues found that over two-thirds (67%) of a sample of 301 regular amphetamine users interviewed in Sydney, Australia had injected amphetamines during the six months prior to interview.

The incidence of unsafe sexual behaviour, which also places individuals at risk of blood borne viruses such as HIV or hepatitis C, is higher in amphetamine users in comparison to heroin users (Klee, 1993). Additionally, a strong connection between methamphetamine use and high-risk sexual behaviour was identified

among a sample of gay and bisexual male methamphetamine users in Los Angeles (Frosch, Shoptaw, Huber, Rawson & Ling, 1996). Almost two-thirds (62%) of the subjects in this study reported engaging in anal sex without a condom during the 12 months prior to treatment. Thus, amphetamine users, particularly those who inject and/or engage in unsafe sexual practices are at high risk of contracting a blood borne virus.

1.17.2. Neurophysiological changes

A number of neurophysiological changes have been identified following amphetamine use. For example, evidence has emerged regarding changes to serotonergic and dopaminergic neuronal pathways in animal models (Woolverton, Ricaurte, Forno & Seiden, 1989; Johnson, Sonsalla, Letter, Hanson & Gibb, 1994) and humans (Volkow, Chang, Wang, Fowler, Leonido-Yee, Franceschi, Sedler, Gatley, Hitzemann, Ding, Logan, Wong & Miller, 2001). Using positron emission tomography scans, Volkow and colleagues found significant dopamine transporter reduction in the striatum of methamphetamine users relative to healthy subjects. This reduction was evident even in methamphetamine users who had been abstinent for at least 11 months and was associated with motor slowing and memory impairment (Volkow *et al.*, 2001).

Further studies have indicated that these effects may be partially reversible with protracted abstinence (12 – 17 months) (Volkow, Chang, Wang, Fowler, Franceschi, Sedler, Gatley, Miller, Hitzemann, Ding & Logan, 2001). However, despite a partial recovery of function, there was no significant improvement in performance on some of the neuropsychological tests for which an association with dopamine transporters was observed. Further work by the same group found significantly greater thalamic, but not striatal, metabolism following protracted abstinence (12 – 17 months) in comparison to subjects with an abstinence interval of less than six months. There was an improvement in performance of motor and verbal memory tests associated with the increase in thalamic metabolism. However, the relative decrease in striatal metabolism in methamphetamine users was longer lasting (Wang, Volkow, Chang, Miller, Sedler, Hitzemann, Zhu, Logan, Ma & Fowler, 2004). Thus, the available evidence suggests that while a

substantial period of abstinence may reverse some of the methamphetamine-induced alterations in brain function, other deficits persist.

1.17.3. Depression

The occurrence of depression in stimulant-dependent individuals is substantially higher than in the general community (Kosten *et al.*, 1998) and depressive symptoms are considered a core criterion for the diagnosis of amphetamine withdrawal (DSM-IV-TR, 2000). Over half (59%) of a sample of amphetamine users attending outpatient clinics in South Wales (Cantwell & McBride, 1998) and almost two-thirds (64%) of noninjecting amphetamine users in California (Domier *et al.*, 2000) reported feelings of depression. Another study found that 40% of a sample of regular (at least twice a month) amphetamine users met the criteria for moderate to severe depression and that higher levels of depression were positively related to the intensity of amphetamine use (Semple, Patterson & Grant, 2005). Further, depression in methamphetamine users may persist for several years following treatment even where drug use is reduced (Rawson *et al.*, 2002). In an early series of case studies on four 'moderate' amphetamine users, all experienced depression that peaked at 48 – 72 hours following the last amphetamine dose (Watson *et al.*, 1972). The single subject from this study who was followed up long term suffered persistent depression for several months, although still being able to function in a home environment during this time.

1.17.4. Psychiatric symptoms related to amphetamine use

Studies of amphetamine users in different countries have provided extensive evidence of a high prevalence of psychiatric symptoms among amphetamine users. In Australia, Vincent and colleagues (Vincent *et al.*, 1998) identified a relationship between mental health problems in a sample of current amphetamine users, including hallucinations and paranoia, and four factors: (1) greater severity of dependence on amphetamines, (2) greater number of mental health symptoms experienced prior to commencing amphetamine use, (3) greater intensity of amphetamine use, and (4) greater number of days of recent benzodiazepine use. In this sample, mental health problems associated with amphetamine use were related not only to direct consequences of regular use such as dependence, but to

pre-existing conditions and concurrent use of other drugs such as benzodiazepines.

In a large (*n* = 1,580) forensic sample in the United States, 11% (*n* = 170) were assessed as currently dependent on amphetamines (Kalechstein, Newton, Longshore, Anglin, van Gorp & Gawin, 2000). In this study, more of the amphetamine dependent group reported violent behaviour, depressive symptoms and suicidal ideation during the previous year in comparison to individuals denying methamphetamine dependence, even after controlling for demographic variables and dependence on other drugs. Amphetamine-dependent individuals also were more likely to report a need for psychiatric assistance at the time of the interview (Kalechstein *et al.*, 2000).

In a more recent Australian report, almost half (49%) of a sample of current amphetamine users reported that they had been diagnosed or treated for a mental health problem and that these problems occurred commonly after the commencement of regular amphetamine use (Baker, Lee, Claire, Lewin, Grant, Pohlman, Saunders, Kay-Lambkin, Constable, Jenner & Carr, 2004).

The Methamphetamine Treatment Project, conducted at eight sites in three American States (California, Montana and Hawaii) provided information from 1016 amphetamine-dependent, treatment-seeking outpatients (Zweben *et al.*, 2004). This study found that 26% of those interviewed had been admitted to a psychiatric facility at some time and 32% had been prescribed psychiatric medication at some point in their lives. Depression was the major psychiatric symptom reported; 50% of male and 68% of female patients reported a history of depression at some point in their lives. Over one-quarter (27%) of the whole sample had attempted suicide (Zweben *et al.*, 2004).

The occurrence of psychosis among regular users of amphetamines has been well documented (Davis & Schlemmer, 1980). Amphetamine psychosis is characterised by delusions of persecution, auditory hallucinations, strange or unusual beliefs, thought reading, visual hallucinations, delusions of reference and thought insertion (Srisurapanont, Ali, Marsden, Sunga, Wada & Monteiro, 2003). While the incidence of amphetamine psychosis is related to the high frequency

use of high doses (Hall *et al.*, 1996), both incidence and severity are related to dosage and route of administration, particularly rapid routes of administration such as injecting and inhalation of vapour (Davis & Schlemmer, 1980; King & Ellinwood, 1997; Batki & Harris, 2004).

While amphetamine psychosis usually abates rapidly (within days) with the cessation of amphetamine intake and the elimination of amphetamines (Jonsson & Sjostrom, 1970), in some cases amphetamine psychosis may persist for several years (Sato, Numachi & Hamamura, 1992) and around 5 – 15% of the users who develop an amphetamine psychosis fail to recover completely (Hofmann, 1983). Furthermore, once the psychotic state develops with amphetamine use, recurrence can happen in response to psychological stressors even in the absence of further amphetamine use (Sato, Chen, Akiyama & Otsuki, 1983). The mechanism by which stimulants produce psychosis is not yet clear, but similarities have been proposed between behavioural sensitisation to stimulants in animals, stimulant-induced psychosis in humans, and chronic schizophrenia (Laruelle, 2000; Ujike, 2002).

1.17.5. Criminal behaviour and violence

Amphetamine use has been associated with criminal activity and aggression in different study populations. In a UK study, 47% of amphetamine users interviewed had committed a violent crime, and half of them associated the violence with their amphetamine use. In addition, 62% reported ongoing problems with aggression that were related to their amphetamine use (Wright & Klee, 2001). Significant associations between violence and the frequency of cocaine and amphetamine use have also been identified in other populations such as Canadian high school students (Smart, Mann & Tyson, 1997). In the United States, 11% of a large forensic sample was assessed as being amphetamine dependent (Kalechstein *et al.*, 2000) while 43% of a large treatment-seeking sample of amphetamine users reported a history of violent behavioural problems (Zweben *et al.*, 2004).

1.18. Summary

The problem of illicit psychostimulant use is a global one (United Nations Office on Drugs and Crime, 2003). Despite the widespread illicit use of amphetamines and

the substantial problems associated with their use (Srisurapanont *et al.*, 2003; Baker *et al.*, 2004), until recently few users sought help from treatment agencies. The reluctance to access treatment may be due to a perception that treatment agencies and programs have developed to meet the needs of opioid users and have little to offer amphetamine users seeking to modify their drug use (Pates & Mitchell, 1996; Wright & Klee, 1999). The reluctance of amphetamine users to avail themselves of opportunities for treatment is of concern in view of the evidence for the effectiveness of general drug treatment (Gerstein & Harwood, 1990; Simpson, 1997; Leshner, 1999; Gowing *et al.*, 2001; Prendergast, Podus, Chang & Urada, 2002).

Although the existence of an amphetamine dependence syndrome has been established (Churchill *et al.*, 1993; Topp & Darke, 1997; Topp & Mattick, 1997, 1997), there is a paucity of empirical data on which to base effective treatments. Further, the natural history of amphetamine withdrawal is still poorly understood despite a small number of studies which have provided limited information on withdrawal symptoms over time (Watson *et al.*, 1972; Gossop *et al.*, 1982; Srisurapanont *et al.*, 1999). The recent failure of an exhaustive review of the literature to find any studies describing the natural history of amphetamine withdrawal points to the need for empirical data in this area (Baker *et al.*, 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, von Mayrhauser & Anglin, 2000). In the absence of an established treatment for amphetamine dependence and/or withdrawal, current treatment approaches to amphetamine withdrawal usually involve symptomatic relief of presenting symptoms and/or various forms of psychotherapy. Substitution therapy is a less common approach. While a number of authors have indicated a need to develop effective treatments (Klee, 1992; Schuckit *et al.*, 1999) an important first step in the development of such treatment is the mapping of the time course and severity of amphetamine withdrawal symptoms. This information would facilitate the timely administration of appropriate interventions aimed at specific symptoms.

1.19. Aims of the study

The focus of this work was on the identification, measurement and treatment of the symptoms experienced by dependent amphetamine users on cessation of regular use – the amphetamine withdrawal syndrome. The specific aims of the study were to:

i) map the nature, time course and severity of signs and symptoms which emerge on cessation of regular amphetamine use in dependent users undergoing inpatient withdrawal treatment

ii) develop and test a valid and reliable instrument suitable for measuring amphetamine withdrawal symptoms

iii) identify and test a range of pharmacological treatments aimed at ameliorating amphetamine withdrawal symptoms.

The process of meeting these aims is described in the following chapters. **Chapters 2** and **3** provide detailed information on the process and outcomes involved in mapping the nature, time course and severity of amphetamine withdrawal symptoms experienced by dependent users in the first one to three weeks of abstinence. **Chapter 4** describes the development and testing of a new instrument designed to measure the amphetamine withdrawal syndrome. **Chapter 5** details the process of identifying and evaluating safe, well tolerated pharmacotherapies for the treatment of acute amphetamine withdrawal symptoms. Finally, the entire work is summarised and conclusions provided in **Chapter 6**.

The experimental work in this series of studies was conducted in two countries, Australia and Thailand. The first of the amphetamine withdrawal studies, described in the following chapter, was conducted in Australia.

2.   CHAPTER 2: AMPHETAMINE WITHDRAWAL STUDY, AUSTRALIA

2.1. Introduction

As noted in **Chapter 1**, the problem of illicit psychostimulant illicit use has reached global proportions (United Nations Office on Drugs and Crime, 2003), with the abuse of amphetamine-type stimulants or cocaine being second only to cannabis in terms of the prevalence of use (Costa e Silva, 2002). However, despite the widespread illicit use of amphetamines and the substantial problems associated with their use, there is no established treatment protocol for the management of the amphetamine withdrawal syndrome (Srisurapanont *et al.*, 2003; Baker *et al.*, 2004).

It was not until recent years that amphetamine users sought help from treatment agencies. This failure to attract amphetamine users into treatment may be due to a perception that treatment programs are oriented toward the needs of opioid users and have little to offer amphetamine users seeking treatment (Pates & Mitchell, 1996; Wright & Klee, 1999). Given the evidence for the general efficacy of substance dependence treatment (Gerstein & Harwood, 1990; Simpson, 1997; Leshner, 1999; Gowing *et al.*, 2001; Prendergast *et al.*, 2002), the perceived failure of services to attract amphetamine dependent individuals is of concern. Further, the failure to manage amphetamine withdrawal symptoms during treatment may contribute to the high rates of relapse among treatment samples (Brecht *et al.*, 2000).

The natural history of amphetamine withdrawal is still poorly understood despite a small number of studies which have provided limited information on withdrawal symptoms over time (Watson *et al.*, 1972; Gossop *et al.*, 1982; Srisurapanont *et al.*, 1999). The recent failure of an exhaustive review of the literature to find any studies describing the natural history of amphetamine withdrawal points to the need for empirical data in this area (Jenner & Saunders, 2004). The absence of empirical evidence on which to base effective treatments may result in the application and delivery of treatments, which may or may not be effective.

To date, there is no established pharmacological treatment for the management of amphetamine dependence and withdrawal (Srisurapanont *et al.*, 2003). While the

recent development of targeted psychosocial approaches for amphetamine dependence (Baker *et al.*, 2001; Rawson *et al.*, 2004) has provided clinicians with a useful tool for the management of amphetamine dependence in outpatients, little research effort has been directed towards the measurement and/or management of withdrawal symptoms in the early period of abstinence. Current treatment approaches include the use of benzodiazepines, antipsychotics and/or antidepressants.

While a range of pharmacotherapies have been developed for the treatment of opioid dependence (Gowing, Ali & White, 2002), currently there is no effective agonist therapy available for amphetamine users. In the absence of an effective agonist maintenance therapy, one of the important first steps in drug treatment is management of withdrawal. If withdrawal symptoms are not treated effectively then rates of relapse in the first days or weeks of treatment may be very high. Effective treatment needs to be based on a sound understanding of the nature and time course of withdrawal, but to date, studies of amphetamine withdrawal phenomena are scarce.

2.1.1. The nature of amphetamine withdrawal

As noted in **Chapter 1**, the fourth edition of the DSM (DSM-IV-TR, 2000) has provided a set of clinically derived criteria for characterising amphetamine withdrawal of which dysphoric mood is a prerequisite symptom. Other criteria for the diagnosis of amphetamine withdrawal are fatigue, vivid, unpleasant dreams, insomnia or hypersomnia, increased appetite and psychomotor retardation or agitation. The DSM-IV also refers to the occurrence of a 'crash' characterised by intense and unpleasant feelings of lassitude and depression that generally require several days of rest (DSM-IV-TR, 2000).

While the prevalence of withdrawal symptoms among amphetamine users has been reported (Churchill *et al.*, 1993; Topp & Mattick, 1997) there is little information on the nature, time course and severity of specific amphetamine withdrawal symptoms. A retrospective study of 50 dependent amphetamine users in the United Kingdom, by Cantwell and McBride found that the majority (86%) had experienced significant withdrawal symptoms on cessation of regular

amphetamine use (Cantwell & McBride, 1998). These symptoms included: irritability (78%); aches and pains (58%); depression (50%); impaired social functioning (46%); shivers and cold sweats (36%); difficulty sleeping (32%); exhaustion (22%); nausea and vomiting (16%); headaches (14%); difficulty in staying awake and increased appetite (12%); constipation (10%); decreased appetite (8%); diarrhoea (6%); increased persecutory ideation, auditory hallucinations and skin irritation (2%). Participants in the UK study had used a variety of psychoactive substances to manage these symptoms, principally benzodiazepines (32%), cannabis (27%), alcohol (21%) and opiates (15%) (Cantwell & McBride, 1998). While this study provided valuable information on the type of symptoms experienced during amphetamine withdrawal, there was no examination of the time course, severity or duration of withdrawal symptoms.

The findings of the UK study by Cantwell and McBride support other evidence indicating that dysphoria or depressive symptoms are commonly identified in both community and treatment samples of amphetamine users (Watson *et al.*, 1972; Cantwell & McBride, 1998; Kosten *et al.*, 1998; Domier *et al.*, 2000; Rawson *et al.*, 2002).

2.1.2. Amphetamine craving

Craving for amphetamines is regarded as a major feature of amphetamine withdrawal, contributing to the likelihood of relapse. However, there is mixed evidence of the relationship between craving states and subsequent drug use. An extensive review of the literature identified an overall modest correlation of 0.4 between reports of craving and substance use (Tiffany, 1990). Conversely, Hartz and colleagues showed that when measured prospectively, craving was an important predictor in continued amphetamine use for patients in treatment (Hartz *et al.*, 2001). Using a prospective, repeated-measures, within-subjects design, these authors found that craving intensity (measured on a visual analogue scale) significantly predicted amphetamine use in the week immediately following each craving report, even when controlling for other variables (i.e., pharmacological intervention, and amphetamine use during the prior week).

2.1.3.   Time course of amphetamine withdrawal

The acute phase of amphetamine withdrawal is thought to last for around 5 – 7 days, although some of the symptoms may continue for weeks or months (Watson *et al.*, 1972; Gossop *et al.*, 1982; Hofmann, 1983). Clinical reports suggest that most amphetamine users experience an initial 'crash' period of around three days following the cessation of dependent amphetamine use. While the individual may sleep for much of the time during the crash phase, clinical reports and at least some studies (Watson *et al.*, 1972; Gossop *et al.*, 1982; Hofmann, 1983) suggest that the crash may be followed by several weeks of insomnia or disturbed sleep accompanied by nightmares.

A review of the literature yielded only two studies that provided information on changes in amphetamine withdrawal symptoms over time. In the first study, conducted in 1982, Gossop and colleagues investigated sleep duration in hospitalised amphetamine users (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 study period of 20 days. While hours of sleep for amphetamine users were greater than or similar to controls on nights 1 – 5, amphetamine users slept less than controls on nights 6 – 20 when the study ended. Night time sleep among the amphetamine users peaked at just over eight hours on the second night and fell thereafter to a low of around five hours on the ninth night since admission. By the 20th night, amphetamine users in this study were sleeping around six hours per night.

While interesting, these data do not provide support for clinical reports of a 'crash' period of several days following cessation of amphetamine use, rather an initial period of 'normal' sleep followed by a prolonged period (at least 15 days) of relative insomnia. Although this study yielded valuable information on the sleep patterns of amphetamine users in the initial three weeks of abstinence, no data on the intensity or frequency of amphetamine use was reported and no other withdrawal symptoms were measured.

The second study systematically examined a range of amphetamine withdrawal symptoms (based on the DSM-IV criteria) over three time points during treatment

for amphetamine withdrawal (Srisurapanont *et al.*, 1999). In a randomised, placebo-controlled, double blind study, Srisurapanont and colleagues examined the benefits of amineptine in treating amphetamine withdrawal. In comparison to controls, the amineptine group showed significant reductions in three symptoms, fatigue, increased appetite and sleep, at the end of the first and second week of treatment. However, amineptine has since been withdrawn from sale due to reports of abuse.

While this trial provided valuable information on amphetamine withdrawal treatment, symptoms in this study were measured at only three time points, each one week apart. Additionally, assessment time points were determined by the time of admission for inpatient treatment rather than being anchored to the time of last amphetamine use.

2.1.4. Summary

There is a clear need for specific information regarding the nature, time course and severity of amphetamine withdrawal symptoms, particularly in the early phase of abstinence. Empirical evidence of the nature of the amphetamine withdrawal syndrome would inform the development of timely and effective interventions and increase the range of options available to clients seeking treatment for amphetamine dependence and withdrawal.

2.1.5. Australian withdrawal study: aims

The aims of the Australian withdrawal study were to identify and measure symptoms arising in the first week of abstinence in a sample of amphetamine-dependent inpatients, specifically to:

   i) quantify the severity of amphetamine withdrawal symptoms during the first week of abstinence

   ii) investigate the time course of amphetamine withdrawal symptoms during the first week of abstinence

2.2. Method

2.2.1. Study Design

Repeated measures, cross-sectional design

2.2.2. Study Setting

The setting for the Australian withdrawal study was a publicly funded substance use facility (Warinilla Clinic) administered by Drug and Alcohol Services South Australia (DASSA). This South Australian State Government funded treatment facility is located in metropolitan Adelaide, South Australia. Treatment is provided free of charge to all clients. This substance use facility includes a pharmacotherapies unit (including a pharmacy), an outpatient clinic, an assessment unit and a 12 bed inpatient unit. Participants in the study were drawn from the inpatient population of this clinic.

2.2.3. Timeframe of data collection

Data collection took place at the inpatient unit of Warinilla Clinic, Adelaide over a six month period between November 2001 and April 2002.

2.2.4. Ethical considerations

The University of Adelaide Human Research Ethics Committee provided ethics approval.

2.2.5. Sample size

Sample size for the present study was based on previous work measuring amphetamine withdrawal symptoms over time and similar studies into the time course and severity of cocaine withdrawal symptoms. As noted in **Section 2.1.3 above**, only two studies that have measured amphetamine withdrawal symptoms over time have been published. In the earlier study, group sample sizes of $n = 20$ each provided adequate power to identify significant differences between experimental and control groups in hours of sleep (Gossop *et al.*, 1982). The second published study was conducted in Thailand. This trial had group sample sizes of $n = 22$, a size which provided enough power to identify significant

differences in withdrawal symptoms measured at three time points over a three week period (Srisurapanont *et al.*, 1999). Two inpatient studies mapping cocaine withdrawal symptoms had group sample sizes of 22 (Satel *et al.*, 1991) and 12 (Weddington *et al.*, 1990). Both of these cocaine withdrawal studies found significant changes over time in newly abstinent cocaine users. Given the overall aims of the present study (to map the nature, time course and severity of amphetamine withdrawal) a sample of around 20 subjects was considered adequate.

2.2.6. Study subjects

Consecutive admissions to Warinilla Clinic, Adelaide, Australia for amphetamine withdrawal treatment were assessed for consistency with the study criteria. Following the completion of the standard clinic nursing and medical admission process and following consultation with the clinical staff, patients were screened for participation in the study. That is, clients were only approached once they had completed the standard clinic admission process. There was no reimbursement for study participation.

2.2.7. Study criteria

The study sample comprised individuals admitted for the treatment of amphetamine dependence who fulfilled the following criteria:

2.2.7.1. Inclusion criteria

2.2.7.1.1. Aged 18 – 45 years

2.2.7.1.2. Urine positive for amphetamines

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

2.2.7.2. Exclusion criteria

2.2.7.2.1. Concurrent acute medical or psychiatric illness requiring psychotropic medication or acute care hospitalisation

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

2.2.7.2.3. Fulfils the DSM-IV diagnostic criteria for other substance dependence, except nicotine

2.2.7.3. Discontinuation criteria

2.2.7.3.1. Use of non-prescribed medications

2.2.7.3.2. Development of a condition requiring psychotropic medications (in addition to the standard psychotropic medications used in amphetamine withdrawal treatment at Warinilla Clinic)

2.2.7.3.3. Development of condition requiring treatment in an acute care medical or psychiatric institution

2.2.8. Study Instruments

A number of instruments were used at different time points to assess variables of interest in this study.

2.2.8.1. Instruments administered on admission

2.2.8.1.1. Mini International Neuropsychiatric Interview (MINI) (Sheehan, Lecrubier, Harnett-Sheehan, Janavs, Weiller, Bonara, Keskiner, Schinka, Knapp, Sheehan & Dunbar, 1997) (Modules for amphetamine and other substance dependence)

The MINI was administered on admission to the study to both screen clients for dependent levels of amphetamine use and to exclude those clients who fulfilled the dependence criteria for other substances (with the exception of nicotine). The MINI utilises the DSM-IV criteria for dependence (range 1 – 7) which is designed to assess a range of psychosocial and physiological aspects of dependence. A score ≥ 3 is indicative of dependence on the substance being assessed.

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

This document was used to assess demographic data, drug use and treatment history for eligible participants.

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

The five item SDS scale (range 0 – 15) provided a measure of the psychological dimensions of amphetamine dependence and to identify the proportion of subjects who had a clinically significant dependence (indicated by a score of >4) (Topp & Mattick, 1997). A score of greater than four on the SDS (using a ROC analysis) was considered to be the best trade-off between sensitivity and specificity when calibrated against the presence or absence of a DSM-III-R diagnosis of severe amphetamine dependence. Therefore an SDS score >4 is indicative of problematic amphetamine use (see Topp & Mattick, 1997). This scale provided an alternative measure of dependence to the DSM-IV criteria, one that was more psychologically orientated.

2.2.8.1.4. Beck Depression Inventory II (BDI) (Beck, Steer & Brown, 1996)

The BDI is a widely used measure of current depression consisting of 21 items, each item consisting of four graded statements relating to how the individual has been feeling in the previous two weeks. Statements are ordered 0 – 3 to show increasing severity of depressive symptoms. Aggregate score range is 0 – 63. All BDI items are clinically derived and have undergone extensive reliability and validity testing. Internal consistency reliability is reported as >.90 (Beck, 1976). The manual for the BDI provides cut off scores which group the severity of depression into four categories: Minimal = 0 – 13, Mild = 14 – 19, Moderate = 20 – 28 and Severe = 29 – 63.

2.2.8.2. *Instruments administered daily during the first week of abstinence*

The following instruments were administered once per day during the first week of abstinence.

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

The AWQ is a 10 item, self-completed instrument that measured the domains of amphetamine craving, sadness, anhedonia, appetite, fatigue, agitation, anxiety, sleep, vivid, unpleasant dreams and motor retardation over the previous 24 hours. Responses to individual items were scored on a range of 0 – 4: 0 = 'not at all'; 1 = 'very little'; 2 = 'a little'; 3 = 'quite a lot'; 4 = 'very much'. The possible range of aggregate scores was 0 – 40 with higher numbers indicating greater severity. Factor analysis of the AWQ yielded a three-factor model: hyperarousal, reversed vegetative and anxiety factors (Srisurapanont *et al.*, 1999). The only other available scale was the SAmDQ. However, although the SAmDQ incorporates some items assessing withdrawal symptoms, its principal function is the assessment of amphetamine dependence.

2.2.8.2.2. Modified version of the Cocaine Selective Severity Assessment scale (Kampman, Volpicelli, McGinnis, Alterman, Weinrieb, D'Angelo & Epperson, 1998)

A modified version of the Cocaine Selective Severity Assessment scale (CSSA) (Kampman *et al.*, 1998) was used to provide information on a broader range of symptoms than that assessed by the AWQ. The interviewer-administered CSSA is a reliable and valid measure of cocaine abstinence symptoms. Given that the DSM-IV lists the same symptoms for cocaine and amphetamine withdrawal it was considered that this scale could be modified for use in amphetamine withdrawal.

Modification of the CSSA involved replacing 'cocaine' with 'amphetamine' to produce the Amphetamine Selective Severity Assessment scale (ASSA). Domains assessed by this 18 item scale included those addressed by the AWQ (with the exception of psychomotor retardation, agitation and vivid dreams) plus decreased

appetite and sleep, craving for carbohydrate (including craving for sweet food and/or drinks), bradycardia, concentration, irritability, paranoid and suicidal ideation, tension and inactivity (item score range 0 – 7, higher scores indicated greater severity). Craving intensity and frequency are measured on this scale by two 0 – 7 cm visual analogue scales.

2.2.8.2.3. St Mary's Hospital Sleep Questionnaire (SMHSQ) (Ellis, Johns, Lancaster, Raptopoulos, Angelopoulos & Priest, 1981)

The SMHSQ, a 14 item, self-completed instrument was completed daily to identify the experience of a 'crash' and to provide detailed and systematic information on subjective sleep parameters. The SMHSQ has shown satisfactory reliability for use with psychiatric and medical inpatients (Ellis *et al.*, 1981; Leigh, Bird, Hindmarch, Constable & Wright, 1988) and has been utilised in studies of cocaine withdrawal (Weddington *et al.*, 1990; Coffey, Dansky, Carrigan & Brady, 2000). Domains assessed by the SMHSQ include hours of night and daytime sleep, sleep depth, quality of sleep, sleep satisfaction, clearheadedness on arising, number of times awake during the night and sleep latency.

2.2.8.2.4. Estimation of hours of sleep in the previous week

Subjects were also asked to provide an estimation of the total number of hours of sleep in the week prior to admission for comparison with sleep variables in the first week of abstinence. To provide a comparison with subjects' estimation of sleep duration, hours of night time sleep were estimated from hourly observations made by nursing staff during the night.

2.2.8.2.5. Modified version of the Cocaine Craving Questionnaire (Tiffany, Singleton, Haertzen & Henningfield, 1993)

Detailed information was also sought in relation to craving for amphetamine during withdrawal. Reportedly, craving is a key feature of withdrawal and has been associated empirically with stimulant use during treatment (Hartz *et al.*, 2001). In the absence of a valid measure of amphetamine craving, a modified version of the Cocaine Craving Questionnaire (Tiffany *et al.*, 1993) was used. This 45 item, self-

completed questionnaire (Tiffany *et al.*, 1993) provided a scale total and five subscale scores measuring different dimensions of craving: 1. Desire to use; 2. Intention and planning to use; 3. Anticipation of positive outcome of use; 4. Anticipation of relief from withdrawal or dysphoria and 5. Lack of control over use. As for the ASSA, the only modification made to this self-completed questionnaire was to substitute the word 'amphetamine' for 'cocaine' to become the Amphetamine Craving Questionnaire (ACQ).

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

The identification of an observer-rated measure of withdrawal would potentially be useful in the development, application and evaluation of clinical treatments in amphetamine withdrawal. In this study, nurses completed the Clinical Global Impressions (CGI) scale (Guy, 1976) daily. The CGI is a single item scale assessing the severity of illness on a scale of 0 – 7, higher numbers indicating greater severity.

Nursing staff also recorded the radial pulse, blood pressure and temperature (per axilla) daily for each subject.

2.2.9.   Data collection and collation

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. Therefore, data were collected up to the seventh day of abstinence after which numbers were too low to conduct statistical tests. Questionnaires (i.e. ASSA, AWQ, ACQ, 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 in this study was eight (days 0 – 7).

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 eight days (days 0 – 7) following the last use of amphetamines. However, beyond the first week of abstinence, subject numbers were too low for statistical analysis.

2.2.10. Data analyses

Variations over time were measured using a Linear Mixed Model ANOVA with day of abstinence as the fixed factor. Predictors of continuous variables such as withdrawal severity were identified by linear regression analysis. 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.

2.2.11. Procedure

The Australian amphetamine withdrawal study incorporated the standard clinic protocol currently used for screening Drug and Alcohol Services South Australia (DASSA) clients. Under this protocol, clients may be self-referred for treatment or their doctor or other relevant health professional may refer them. On presentation to the clinic, a clinic staff member from the assessment unit (usually a nurse or social worker) interviews them. This initial interview consists of taking a brief history including, drug use history; drug treatment and withdrawal history; medical and psychiatric history and a psychosocial history.

Following this screening process, clients were offered a range of treatments appropriate for their needs. Where inpatient treatment was deemed an appropriate option, the client's name was placed on a waiting list for admission when a bed became available. Waiting times for admission to the inpatient unit were usually between one and five days depending on the demand for beds.

Clients made daily telephone contact with the inpatient unit to check the availability of a place in the clinic. Once a place became available, they presented for admission to the inpatient unit of Warinilla Campus. The initial admission process

involved an interview with a member of the inpatient nursing staff comprising an extensive history including drug use history; drug treatment and withdrawal history; medical and psychiatric history and a psychosocial history. Following the initial admission process, inpatients underwent a full medical examination by the clinic medical officer. Clients were required by the clinic to provide a sample of urine for drug screening.

If no exclusion criteria had become evident as a result of the nursing admission process and medical examination, the client's name was flagged as a potential study subject. At this point, the potential subject was given a verbal explanation of the study protocol by the author together with the study information sheet and consent form. If the potential subject expressed an interest in joining the study, informed consent to participate was obtained by the author.

All data collection instruments were administered (or supervised, in the case of self-report measures) by the author (CM). Subjects gave written informed consent prior to data collection. Subjects in the study, in common with other clients, received the supportive counselling that is a normal part of inpatient treatment for amphetamine dependence at the clinic.

2.2.11.1. Clinic medication protocols

In the clinic where this study was 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 **Table 2.1**).

Table 2.1   ***Symptomatic medication protocol***

Medication	Indication	Dosage	Route	Frequency
Pericyazine	Agitation	2.5 – 5mg	Oral	Three times a day prn
Diazepam	Anxiety	5 – 10mg	Oral	Four times a day prn
Either Nitrazepam or	Insomnia	5 – 10mg	Oral	At night prn
Temazepam	Insomnia	10 – 20mg	Oral	At night prn
Paracetamol	Analgesia	500 – 1000mg	Oral	Every four hours prn
Naproxen	Analgesia	250mg	Oral	Three times a day prn

Once informed consent was obtained, the screening instruments were administered.

2.2.11.2. Screening for amphetamine and other substance dependence

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

Providing the client was identified as being dependent on amphetamines and or nicotine only, the following admission instruments were administered:

2.2.11.3. Data collection on study admission

2.2.11.3.1. Structured interview schedule assessing drug use and treatment history

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

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

2.2.11.4. Daily measurement of amphetamine withdrawal symptoms

Each subject completed four questionnaires daily (including the day of admission).

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

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

2.2.11.4.3. Modified version of the Cocaine Craving Questionnaire (ACQ) (Tiffany *et al.*, 1993)

2.2.11.4.4. Modified version of the Cocaine Selective Severity Assessment scale (ASSA) (Kampman *et al.*, 1998).

In addition, a member of the clinical staff completed the Clinical Global Impression (CGI) (Guy, 1976) daily in respect of each subject. Each morning, a member of the nursing staff provided an estimate of the number of hours of sleep on the previous night in respect of each subject.

Copies of study instruments are included in **Appendix 1[1]**.

2.3. Results

Of 74 patients who were admitted for treatment of amphetamine dependence during the study period, one refused to participate; three had a psychiatric condition which prevented the provision of informed consent, 42 had concurrent dependence on alcohol and/or cannabis and eight provided a urine sample negative for sympathomimetic amines (a marker for amphetamine use). The final sample comprised 20 subjects who met the inclusion criteria for the study.

Questionnaires were administered once a day and data collated according to the (self-reported) time since last use. That is, as noted in **Section 2.2.9 above**, questionnaire data collected within 24 hours of the last (self-reported) use of

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[1] For copyright reasons it is not possible to reproduce a copy of the BDI

amphetamines was designated 'Day 0'; data collected 24 – 48 hours following the last use of amphetamines was called 'Day 1' etc. Five subjects provided data on Day 0; 12 on Day 1; 13 on Day 2; 14 on day 3; 13 on Day 4; 10 on Days 5 and 6, and 8 on Day 7 of abstinence.

2.3.1. Sample characteristics

Table 2.2 shows the characteristics of the study sample.

Table 2.2   Characteristics of the study sample

Characteristics	(*n* = 20)
Age; mean years (range)	30 (19 – 45)
Female *n* (%)	11 (55)
Unemployed *n* (%)	19 (95)
Married/cohabiting *n* (%)	4 (20)
Education, mean years (SEM)	11 (0.31)
Used every day in the previous month, *n* (%)	10 (50)
Age first used amphetamine; mean years (range)	20 (13 – 32)
Length of regular amphetamine use; mean years (range)	6 (2 – 13)
Days of amphetamine use in the previous month; mean (range)	25 (12 – 30)
Amount (grams) used per day in the previous month; median (range)	0.94 (0.2 – 6)
Amount (AUD$) spent per day on amphetamines; median (range)	$194.70 ($50.00–$400.00)
Total grams used during previous month; median (range)	26 (4 – 126)
Previously treated for amphetamine dependence; *n* (%)	11 (55)

As may be expected in a treatment sample, subjects were principally long-term, high-dose amphetamine users. Over half had previously received treatment for amphetamine dependence and most subjects were single and unemployed.

2.3.2.   Form of amphetamine used

The majority of subjects (15/75%) used amphetamine in its crystalline form. Three subjects (15%) described their amphetamine as a waxy, oily, pasty or gluey substance and one subject each used amphetamine in powder or liquid form.

2.3.3.   Severity of Dependence on Amphetamines: DSM-IV criteria

Overall, the subjects were highly dependent on amphetamines. The mean number of DSM-IV criteria met for amphetamine dependence was 6 (range 4 – 7). A score $\geq$3 on the seven DSM-IV criteria is indicative of dependence on the substance being assessed and was a criterion for inclusion in the study.

2.3.4.   Severity of Dependence on Amphetamines: SDS

The mean score on the Severity of Dependence Scale (SDS) was 10 (range 3 – 15). Of the 20 subjects, 17 (85%) had a score of >4 on the SDS indicating clinically significant dependence on amphetamines (Topp & Mattick, 1997). Analysis of the five individual SDS items showed that only one subject had 'never' or 'almost never' felt that their amphetamine use was out of control; 5 (25%) felt their use was 'sometimes' out of control; 3 (15%) 'often' and 11 (55%) felt that their amphetamine use was 'always' or 'nearly always' out of control during the previous year. Similarly, over half (11 subjects or 55% of the sample) had 'always' or 'nearly always' felt anxious at the prospect of missing a dose; 5 (25%) had 'often' felt anxious; 4 (20%) had 'sometimes' felt anxious and no subject had 'never' felt anxious at the prospect of missing a dose. Only 2 subjects (19%) had been 'not at all' worried about their amphetamine use in the previous year; 5 (25%) had been 'a little' worried; 7 (35%) had worried 'quite a lot' and 6 (30%) had worried 'a great deal'. Only 2 (10%) of subjects had 'never' or 'almost never' wished they could stop using amphetamines during the previous year; 4 (20%) had 'sometimes' wished they could stop; 6 (30%) had 'often' wished they could stop and 8 (40%)

had 'always' or 'nearly always' wished they could stop using amphetamines during the previous year.

Only one subject did not anticipate difficulty in ceasing amphetamine use; 7 (35%) felt it would be 'quite difficult' to cease use; 9 (45%) felt it would be 'very difficult' and 3 (15%) felt it would be 'impossible' to stop or go without amphetamine.

2.3.5. Pattern of other substance use in the month prior to admission

Use of other substances (in addition to amphetamines) in the month prior to admission was assessed. Although subjects were excluded if they were dependent (according to DSM-IV criteria) on other substances (except nicotine), polydrug use was common among the sample. **Table 2.3** shows the extent of other substances used at least once during the month prior to admission.

Table 2.3   Other substances used in the month prior to admission

Substance used	*n* (%)	Days used in the previous month
Tobacco	19 (95)	30
Alcohol	13 (65)	Median (range) 1 (1 – 20)
Cannabis	12 (60)	Mean (SEM) 18.4 (3.8)
Benzodiazepines	6 (30)	Mean (SEM) 14.8 (5.6)
Ecstasy	5 (25)	Median (range) 2 (1 – 12)
Dexamphetamine	4 (20)	Median (range) 1.5 (1 – 30)
Heroin	2 (10)	Median (range) 2 (1 – 3)
Cocaine	2 (10)	1
Non-prescribed methadone	1 (5)	2
Ephedrine	1 (5)	1

The median number of different substance types used in the month prior to treatment (excluding amphetamine) was 4 (range 2 – 7). Most common other substances used were tobacco, alcohol and cannabis respectively. None of the

study subjects had used methylphenidate, hallucinogens, or inhalants in the month prior to admission.

2.3.6. Route of administration

All subjects were current injectors at the time of study. For ten (50%) of the subjects, injection was also the initial route of administration. **Table 2.4** shows the initial and current route of administration (ROA) of amphetamines for study subjects. For those 10 (50%) subjects who had changed the route of administration since first using amphetamines, the median number of years between first amphetamine use and the change to injection as a route of administration was 5 (range <1 year to 16 years).

Table 2.4   Main route of administration of amphetamines

Main route of administration	Initial ROA *n* (%)	Current ROA *n* (%)
Intravenous injection	10 (50)	20 (100)
Oral	2 (10)	0
Nasal	8 (40)	0

2.3.7. Binge use of amphetamines in the previous six months

Amphetamines are commonly used in 'runs' or 'binges'. This study used the definition of a 'binge' defined by the Illicit Drug Reporting System in Australia as using amphetamines continuously, without sleep, for at least 48 hours followed by three or more days off (Topp *et al.*, 2002). Of the 20 subjects, 19 reported having binged on amphetamines during the previous six months. The median length of the longest binge during the previous six months was 5.5 days, range 3 – 14 days. No subject reported binge pattern amphetamine use in the month prior to admission for treatment.

2.3.8. Recency of amphetamine use

The mean number of hours between the last use of amphetamine and initial data collection on admission to the inpatient clinic was 48 (SEM = 6.9) range 3 – 118 hours. The median quantity used at the last use of amphetamine prior to admission to the inpatient clinic was 0.3, range 0.1 – 1.0 gm.

2.3.9. Severity of depression on admission

The mean score on the Beck Depression Inventory II (BDI) was 34.5 (SEM = 3.1) range 10 – 54. **Table 2.5** shows the BDI severity groupings for the sample. The majority of the subjects scored in the severe range of the BDI on admission indicating a high level of depression among the sample.

Table 2.5   Beck Depression Inventory groupings on admission

BDI II Severity groupings	Number	Percentage
Minimal (scoring range 0 – 13)	2	10.5
Mild (scoring range 14 – 19)	1	5.3
Moderate (scoring range 20 – 28)	4	21.1
Severe (scoring range 29 – 63)	12	63.2
Total	19*	100.0

*One subject refused to complete the BDI

2.3.10. Treatment retention

Seven to ten days was the standard length of inpatient treatment for amphetamine withdrawal at the clinic where this study was conducted. For the present study sample, the mean number of days on which subjects remained in the clinic was 6.5 (SEM = 0.6) range 1 – 12 days. Of the 20 subjects in this study, seven (35%) completed amphetamine withdrawal treatment. For the seven subjects who completed treatment, the mean number of days spent in the clinic was 9 (SEM = 0.7, range 7 – 12) days. A further two subjects (10%) required acute care treatment and were transferred to a general hospital (severe inflammation of injection site and ectopic pregnancy). Another seven subjects (37%) discharged

themselves from treatment citing various reasons including boredom, having business to attend to, or deciding to complete the withdrawal process at home. Four subjects (20%) were discharged for breaching clinic rules including threatening behaviour to clinic staff and absconding while on day leave. There were no differences between those who completed the withdrawal process and those who dropped out of treatment on any of the baseline measures (e.g., drug use history, level of dependence, depression) or demographic variables.

2.3.11. Measurement of the time course and severity of withdrawal

The following section describes the time course and severity of withdrawal phenomena measured by the three withdrawal instruments used in this study – the self-completed Amphetamine Withdrawal Questionnaire (AWQ), the interviewer-administered Amphetamine Selective Severity Assessment (ASSA) and the observer-rated Clinical Global Impressions scale (CGI).

2.3.11.1. *Pattern of withdrawal symptoms (AWQ)*

Subjects completed the AWQ daily to assess symptoms experienced over the previous 24 hours. The possible range of scores for the ten individual items was 0 – 4 with higher scores indicating greater severity (possible range of summed scores, 0 – 40). **Figure 2.1** shows the distribution of summed AWQ scores over the first week of abstinence.

**Figure 2.1   *Pattern of withdrawal symptoms (AWQ)***
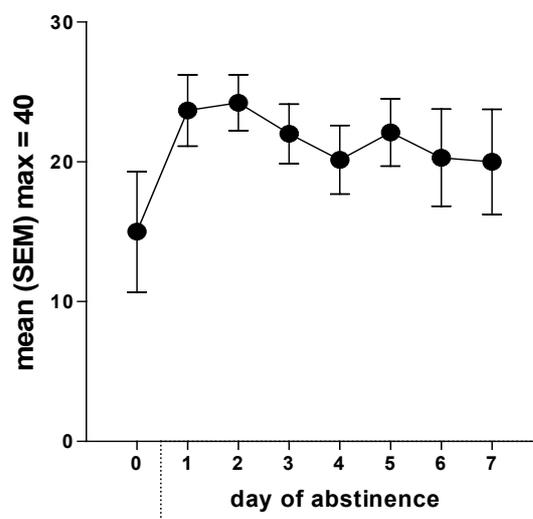
Summed AWQ scores rose rapidly within 48 hours of the last amphetamine use peaking on the first and second days of abstinence. Although the aggregate AWQ score fluctuated during Days 1 – 7 of abstinence, the aggregate score remained elevated in comparison to the initial assessment. There was a trend towards significant change in AWQ scores over the first seven days of abstinence (F = 1.8, df 7,62 p = 0.096).

2.3.11.2. Distribution of individual AWQ items

Distributions of the 10 individual AWQ items are shown in **Figure 2.2**. The possible range of scores for each item was 0 – 4, higher scores indicated greater severity. For clarity, error bars have been omitted and items grouped on graph panels according to the similarity of their distribution.

Symptoms of anxiety and agitation (see **Figure 2.2: Panel 1**) fluctuated during the first week of abstinence. Both were elevated relative to initial scores by the end of the first week of abstinence, although only agitation approached significance (F = 1.8, df 7,62 p = 0.094). In contrast, symptoms of craving for amphetamines and vivid, unpleasant dreams increased from relatively low initial levels to peak at the end of the first week of abstinence (**Figure 2.2: Panel 2**). Of these, only vivid, unpleasant dreams changed significantly (F = 2.2, df 7,61 p = 0.045).

Symptoms of increased sleep, increased appetite and motor retardation (see **Figure 2.2: Panel 3**) increased sharply from low initial levels before returning to near initial levels by the end of the first week of abstinence. Of these symptoms, only increased sleep showed a trend toward significance (F = 2.0, df 7,64 p = 0.075).

Figure 2.2   Distribution of AWQ items
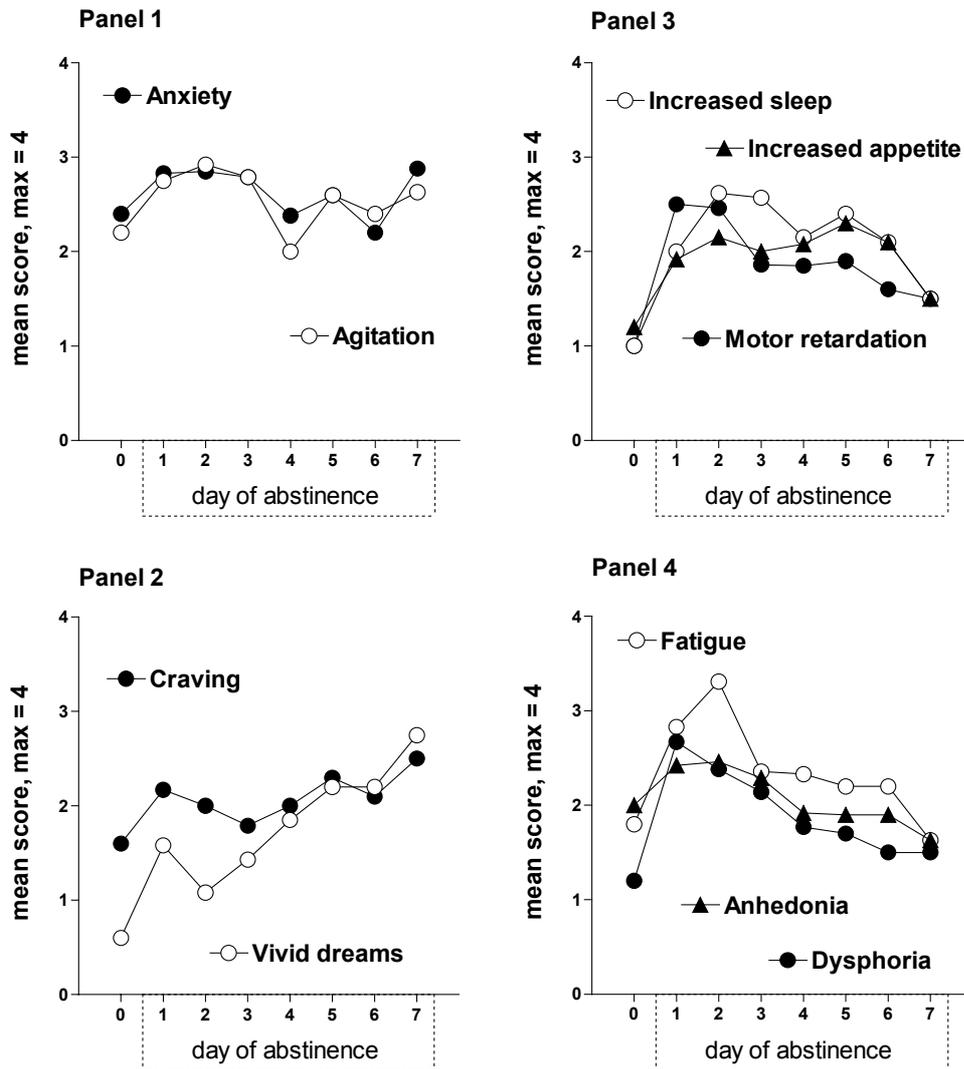
Depression-related symptoms of fatigue, anhedonia and dysphoria (see **Figure 2.2: Panel 4**) peaked in the first two days of abstinence before reducing towards initial levels by the end of the first week. Of these symptoms, only dysphoria (F = 3.0, df 7,62 p = 0.008) and fatigue (F = 2.2, df 7,65 p = 0.037) changed significantly. Therefore, of the ten symptoms measured by the AWQ, three (fatigue, dysphoria and vivid dreams) changed significantly over the first week of abstinence while two (agitation and increased sleep) showed a trend towards significance.

2.3.11.3. Withdrawal symptom severity (AWQ)

Table 2.6 shows the mean and SEM together with the *p* value of change over the study period for the individual AWQ items.

Table 2.6   ***Severity of amphetamine withdrawal symptoms (AWQ items)***

AWQ item (range 0 – 4)	Mean	SEM	*p*
Anxiety	2.63	0.14	*0.464*
Agitation	2.60	0.14	*0.094*
Fatigue	2.42	0.13	*0.037*
Increased sleep	2.16	0.13	*0.075*
Anhedonia	2.10	0.15	*0.607*
Amphetamine craving intensity	2.06	0.15	*0.994*
Increased appetite	2.00	0.14	*0.351*
Dysphoria	1.95	0.14	*0.008*
Motor retardation	1.92	0.14	*0.103*
Vivid, unpleasant dreams	1.71	0.17	*0.045*

During the first week of abstinence, anxiety and agitation showed the greatest severity followed by fatigue and increased sleep. Anhedonia, craving intensity and increased appetite were moderately severe. Less severe but still marked features of withdrawal were symptoms such as dysphoria, motor retardation and vivid, unpleasant dreams.

### 2.3.11.4. Amphetamine Withdrawal Questionnaire Subscales

Factor analysis of the AWQ in previous studies (Srisurapanont *et al.*, 1999) identified three subscales, Hyperarousal Subscale, Anxiety Subscale and the Reversed Vegetative Subscale. Three items each loaded onto these subscales incorporating 9/10 single items (dysphoria loaded across both Hyperarousal and Reversed Vegetative factors). As individual items are scored in the range of 0 – 4,

the possible range of subscales scores was 0 – 12. Distributions of the three AWQ subscales are shown in **Figure 2.3**.

The Reversed Vegetative subscale comprising three items (1) fatigue (2) increased appetite and (3) increased sleep (**Figure 2.3: Panel 1**) increased significantly (F = 2.3, df 7,65 p = 0.03) in the early part of withdrawal before returning towards initial levels by the end of the first week of abstinence (mean = 6.68, SEM = 0.31). Anxiety subscale scores comprising three items (1) anhedonia (2) anxiety and (3) motor retardation (see **Figure 2.3: Panel 2**) remained elevated throughout the study period (mean = 6.73, SEM = 0.38) and did not change significantly (p = 0.22).

The Hyperarousal subscale comprises three items (1) amphetamine craving intensity (2) agitation and (3) vivid, unpleasant dreams (see **Figure 2.3: Panel 3**). Hyperarousal scores increased non-significantly (p = 0.78) over the study period, particularly towards the end of the first week of abstinence (mean = 6.43, SEM = 0.39).

Figure 2.3   Amphetamine Withdrawal Questionnaire Subscales

Panel 1: Reversed Vegetative Subscale

Panel 2: Anxiety Subscale

Panel 3: Hyperarousal Subscale
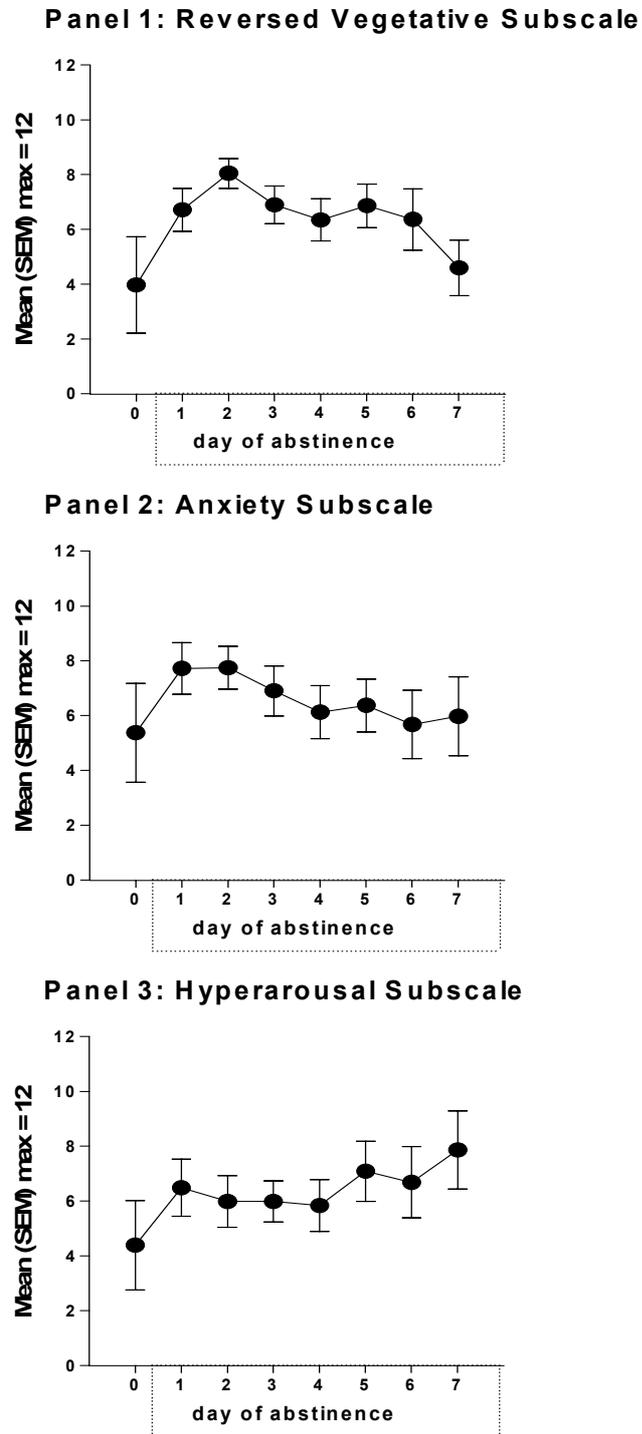
2.3.11.5. Pattern of withdrawal symptoms (ASSA)

The ASSA was administered to subjects daily up to the end of the first week of abstinence by a single researcher (CM). Summed ASSA scores changed significantly during the first week of abstinence (F = 2.7, df 7,64 p = 0.017), peaking at between 48 and 72 hours following the last use of amphetamine before declining to initial levels (within 24 hours of the last use of amphetamines) by the seventh day of abstinence (see **Figure 2.4**).

Figure 2.4   Time course and severity of withdrawal phenomena (ASSA)
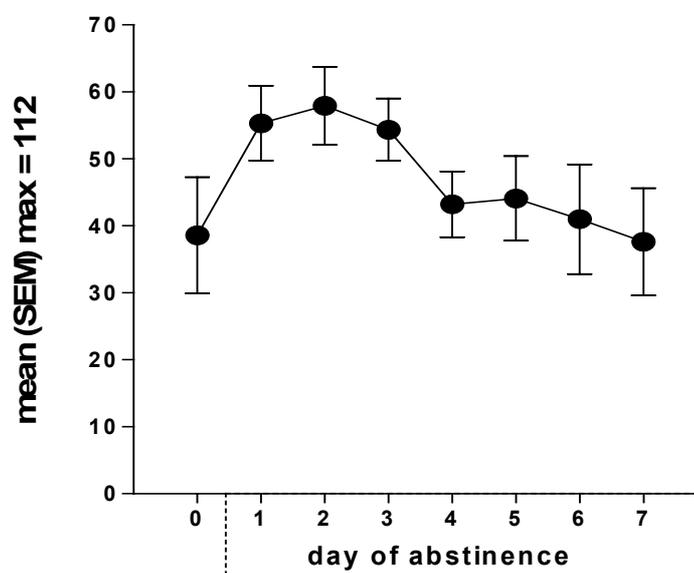
2.3.11.6. Distribution of individual withdrawal symptoms (ASSA)

Distributions of the 18 individual ASSA items are shown in **Figure 2.5**. The possible range of scores for each item was 0 – 7, higher scores indicated greater severity. For clarity, error bars have been omitted and items grouped on graph panels according to the similarity of their distribution.

Irritability, anxiety and tension (see **Figure 2.5: Panel 1**) rose from relatively low initial levels to peak on days two and three of abstinence remaining elevated relative to initial levels for the remainder of the first week. As shown on the same panel, poor concentration peaked somewhat later on day four, returning towards initial levels by the end of the first week of abstinence. Two of these four items,

anxiety (*F* = 2.4, df 7,63 *p* = 0.027) and irritability (*F* = 4.3, df 7,61 *p* < 0.001) changed significantly.

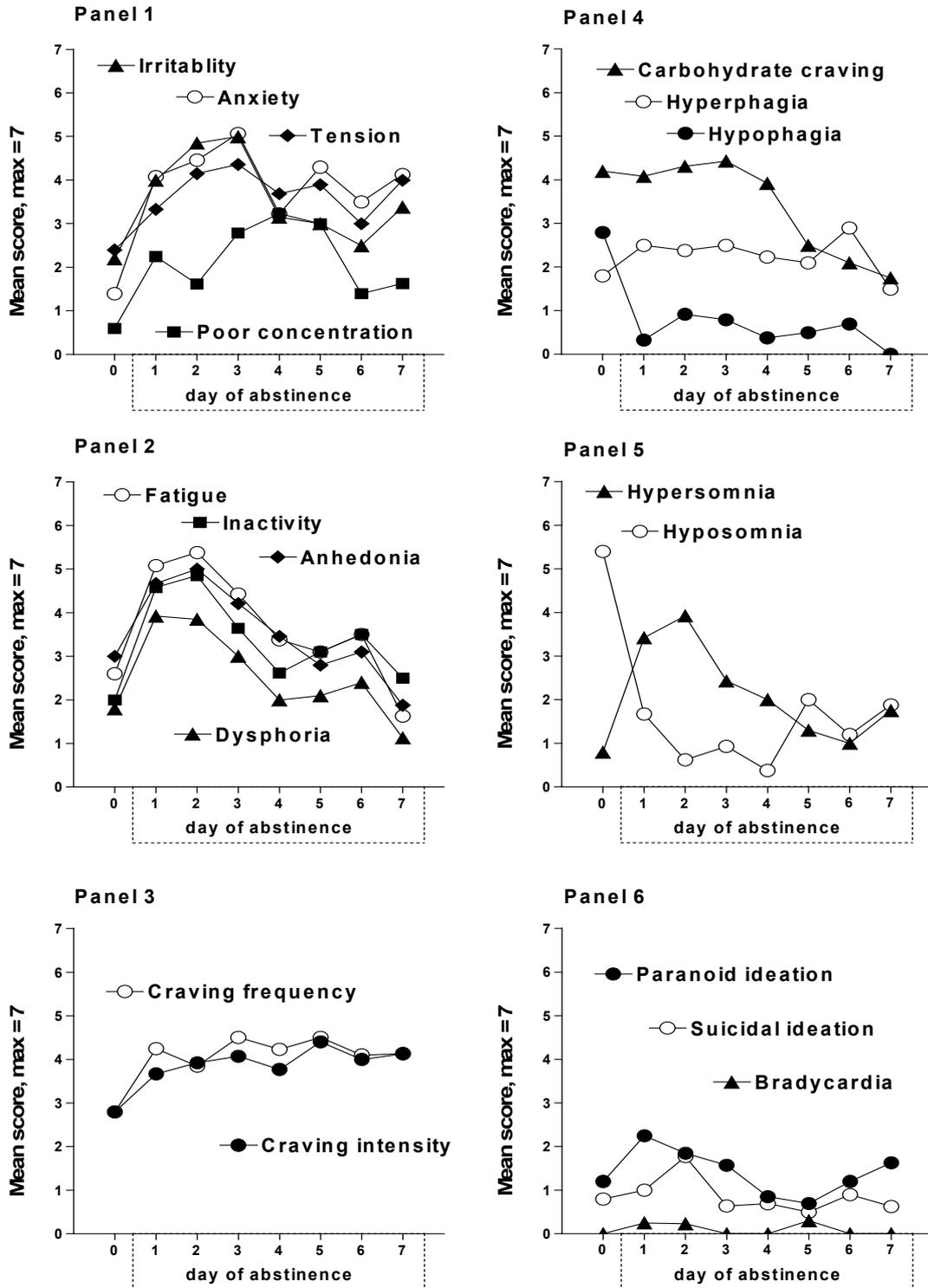### Figure 2.5   Distribution of ASSA items

Figure 2.5: Panel 2 shows the distribution of depression-related items such as fatigue, inactivity, anhedonia and dysphoria. Depression-related symptoms peaked on day two reducing to below initial levels by the end of the first week. Two of these four items, dysphoria (F = 2.1, df 7,64 p = 0.047) and fatigue (F = 2.2, df 7,69 p = 0.042), changed significantly over the first week of abstinence. **Figure 2.5: Panel 3** shows the distribution of craving-related items such as the frequency and intensity of craving for amphetamines, both of which remained elevated throughout the study period showing no significant change.

Figure 2.5: Panel 4 shows the distribution of appetite-related items. Hyperphagia remained relatively stable, but there was a marked decrease in hypophagia in the first 24 – 48 hours of abstinence. The reduction in carbohydrate craving showed a trend towards significance (F = 4.1, df 7,61 p = 0.062). **Figure 2.5: Panel 5** shows the distribution of sleep-related items. Hypersomnia peaked on days one and two of abstinence (non significant). The significant reduction in hyposomnia (F = 4.1, df 7,77 p = 0.001) over the first 24 hours following the last use of amphetamines suggested a residual stimulant effect rather than the onset of a withdrawal symptom.

Paranoid and suicidal ideation (see **Figure 2.5: Panel 6**) remained mild and stable during the first week of abstinence while bradycardia remained at very low levels throughout. None of the items on this panel changed significantly. Therefore, of the 18 ASSA items, five (anxiety, fatigue, irritability, depression and hyposomnia) changed significantly and one (carbohydrate craving) showed a trend towards significant change over the first week of abstinence.

### 2.3.11.7. Withdrawal symptom severity (ASSA)

Table 2.7 shows the mean (SEM) for individual ASSA items together with the *p* value of change over the first week of amphetamine abstinence. Craving (intensity and frequency) and anxiety were the most severe symptoms experienced during the first week of abstinence followed by fatigue, tension, irritability, anhedonia, inactivity and carbohydrate craving respectively. Depression, hyperphagia, poor concentration, paranoid ideation and hypersomnia were relatively milder, while suicidal ideation, hypophagia and bradycardia remained very mild throughout.

Table 2.7   ***Severity of amphetamine withdrawal symptoms (ASSA items)***

ASSA Item (range 0 – 7)	Mean	SEM	*p*
Amphetamine craving frequency	4.14	0.26	*0.844*
Anxiety	3.98	0.27	*0.027*
Amphetamine craving intensity	3.90	0.28	*0.961*
Fatigue	3.87	0.30	*0.042*
Tension	3.71	0.27	*0.348*
Irritability	3.70	0.27	*0.001*
Anhedonia	3.70	0.31	*0.168*
Inactivity	3.51	0.28	*0.144*
Carbohydrate craving	3.51	0.32	*0.062*
Depression	2.68	0.30	*0.047*
Hyperphagia	2.30	0.30	*0.662*
Hypersomnia	2.27	0.31	*0.129*
Poor concentration	2.22	0.26	*0.187*
Paranoid ideation	1.43	0.23	*0.212*
Hyposomnia	1.41	0.23	*0.001*
Suicidal ideation	0.89	0.21	*0.393*
Hypophagia	0.68	0.20	*0.247*
Bradycardia	0.10	0.06	*0.658*

2.3.11.8. Time course and severity of observer-rated withdrawal (CGI)

Observer-rated withdrawal (CGI) peaked on the first day of abstinence remaining elevated in relation to initial measures (with the exception of a dip on the sixth day) for the remainder of the study period (see **Figure 2.6**). There was no significant effect for time in observer-rated withdrawal.

Figure 2.6   Time course and severity of observer-rated withdrawal (CGI)
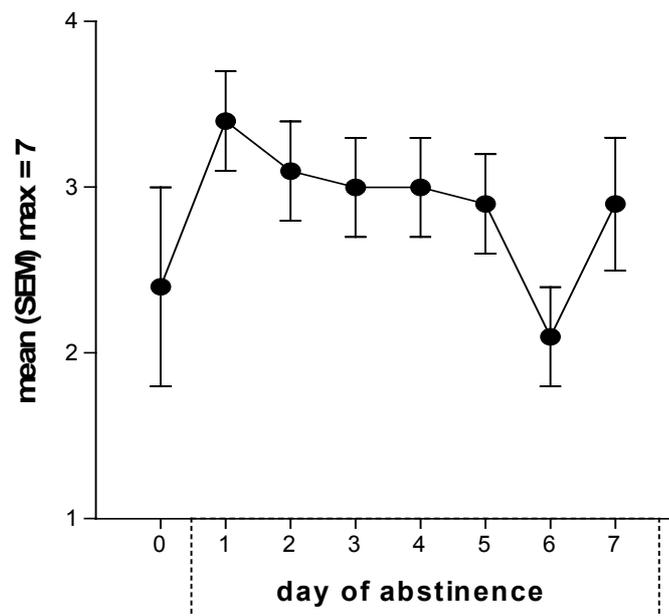
2.3.11.9. Vital signs

Objective measures such as pulse and blood pressure remained within normal limits for the duration of the study period.

2.3.12. Craving for amphetamines (ACQ)

The (self-completed) Amphetamine Craving Questionnaire (ACQ) was used to assess subjects' craving related cognitions and feelings over the previous 24 hours. Reverse scored items were recoded (as per the scale authors' instructions) such that higher scores indicated greater craving. Items were then summed to provide an aggregate score (possible range 45 – 315).

Scores were calculated for the five subscales. Each subscale included nine items scored 1 – 7, therefore, aggregate subscales scores had a possible range of 9 – 63. ACQ subscales included the desire to use amphetamine (mean = 37.55, SEM = 1.47); intention and planning to use amphetamine (mean = 36.94, SEM = 1.29); anticipation of positive outcome of amphetamine use (mean = 42.99, SEM = 1.04); relief from withdrawal or dysphoria (mean = 41.81, SEM = 0.80) and perceived lack of control over amphetamine use (mean = 45.61, SEM = 1.15).

Distribution of the aggregate ACQ and five subscale scores are shown in **Figure 2.7**. Aggregate craving scores had high variability and showed a non-significant increase (F = 1.2, df 7,62 p = 0.294) during the first week of abstinence from amphetamines (see **Figure 2.7: Panel 1**). The pattern of subscale scores (see **Figure 2.7: Panel 2**) was similar to the aggregate craving score. None of the subscales changed significantly over time.

Figure 2.7   Amphetamine Craving: aggregate ACQ and subscale scores
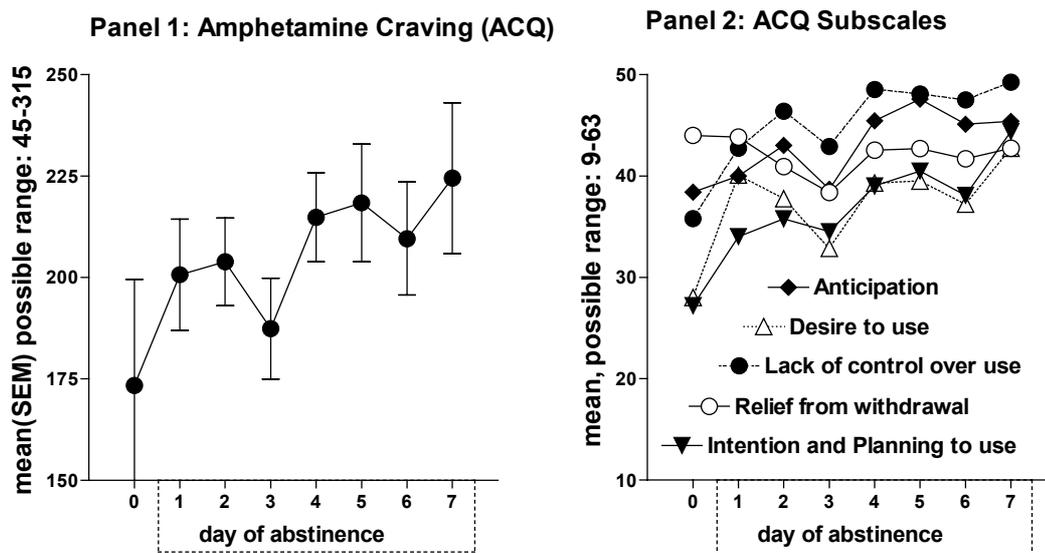
2.3.13. Sleep patterns during the first week of abstinence

Sleep patterns in the previous 24 hours were measured using the St Mary's Hospital Sleep Questionnaire (SMHSQ). Self-reported data on sleep patterns varied during the course of the first week of abstinence. **Figure 2.8** shows the pattern of sleep characteristics during the study period. It should be noted that four of the five subjects for whom data were available within 24 hours of amphetamine use (Day 0) reported no sleep in the previous 24 hours.

The mean number of hours of sleep in one 24 hour period rose from low initial levels on Day 0 to peak on the second day of abstinence (mean = 13.7, SEM = 1.6) hours. Thereafter, hours of sleep reduced gradually until the seventh day of abstinence (mean = 8.8, SEM = 1.1 hours) when data collection ceased (see

Figure 2.8: Panel 1). The change in total hours of sleep was significant (F = 3.9, df 7,66 p = 0.001).

2.3.13.1. Night sleep period

From very low levels on Day 0 (see **Figure 2.8: Panel 1**) self-reported hours of night sleep rose to a peak (mean = 10.1, SEM = 1.3 hours) on Day 2 after which they declined steadily for the remainder of the first week of abstinence (F = 3.9, df 7,70 p = 0.001).

2.3.13.2. Daytime sleep period

Similarly, daytime sleep rose from very low initial levels on Day 0 (see **Figure 2.8: Panel 1**). Hours of daytime sleep rose to a peak (mean = 3.5, SEM = 0.90 hours) on Day 2 after which they declined steadily for the remainder of the first week of abstinence. The change in daytime sleep was non-significant (F = 0.81, df 7,66 p = 0.581).

2.3.13.3. Sleep characteristics

The quality (see **Figure 2.8: Panel 2**), depth (see **Figure 2.8: Panel 3**) and satisfaction with night sleep (see **Figure 2.8: Panel 4**) remained at moderately high levels during the first week of abstinence following a low point on Day 0 (within 24 hours of amphetamine use). Similarly, the number of times awake during the night reduced from around four on Day 0 then remained at a moderate level throughout the first week of abstinence (see **Figure 2.8: Panel 5**).

Clearheadedness on arising (see **Figure 2.8: Panel 6**) was at its lowest point on the night prior to admission but improved steadily over the remainder of the first week of abstinence. None of the sleep characteristics shown in **Figure 2.8: Panels 2 – 6** changed significantly over the first week of abstinence. Sleep latency (data not shown) was highly variable over the study period (median = 10, range 0 – 330 minutes) and did not change significantly (p = 0.183).

Figure 2.8   Sleep patterns and sleep characteristics
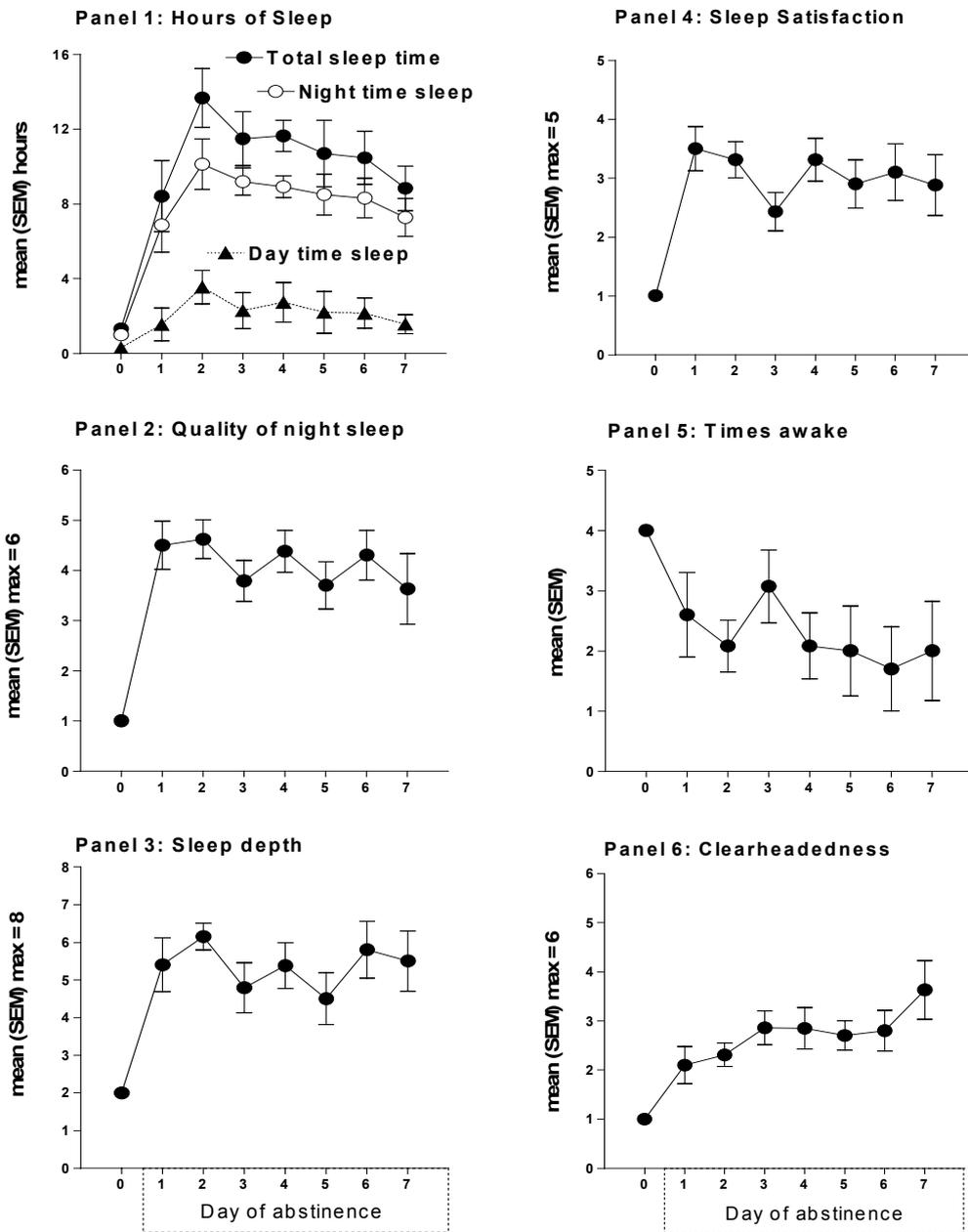
2.3.13.4. Observer-rated measures of sleep

Clinic nursing staff estimated the total number of hours of sleep during the hours of 2300 to 0700 for each night of the study period by recording hourly observations. There was a positive correlation between objective measures of sleep duration

recorded by nursing staff and subjects self-reported hours of sleep during the same time period ($r = 0.44$ $p < 0.01$).

2.3.13.5. Relationship between hours of sleep prior to admission and sleep characteristics during withdrawal

To provide a comparison with sleep patterns during withdrawal, subjects were asked to estimate the total number of hours of sleep (both day and night) during the week (seven days) prior to admission for inpatient treatment. The median number of hours of sleep in the seven days prior to admission was 19, range 5 – 93 hours.

While there was no relationship between hours of sleep in the week prior to admission for treatment and hours of sleep during the acute withdrawal period there were positive correlations between hours of sleep prior to admission and several sleep characteristics. Depth of sleep ($r = 0.33$ $p < 0.01$); quality of sleep ($r = 0.33$ $p < 0.01$); clear-headedness on arising ($r = 0.28$ $p < 0.05$) and satisfaction with sleep ($r = 0.39$ $p < 0.01$) were correlated positively with hours of sleep in the week prior to admission. There was a negative relationship between estimated hours of sleep in the week prior to admission and the number of times subjects woke up during the night ($r = -.23$ $p < 0.05$). Therefore, greater hours of sleep prior to admission were associated with greater quality of some sleep characteristics during withdrawal treatment.

2.3.14. Relationships between instruments used to measure withdrawal

Table 2.8 shows the relationships between summary scores of the AWQ during the first week of abstinence and the interviewer-administered Amphetamine Selective Severity Assessment (ASSA), the Amphetamine Craving Questionnaire (ACQ) and the observer-rated Clinical Global Impressions (CGI) scale. There was a strong positive correlation between the AWQ and the ASSA and a moderately strong positive correlation between the AWQ and the ACQ, indicating satisfactory agreement between these scales. There was a modest but significant positive correlation between the AWQ and the CGI.

Table 2.8   ***Relationships between instruments used to measure withdrawal severity***

Total	AWQ	ASSA	CGI	ACQ
AWQ		0.81	0.34	0.49
ASSA	0.81		0.38	0.39
CGI	0.34	0.38		0.33
ACQ	0.49	0.39	0.33	

All correlations significant at $p < 0.01$

2.3.15. Medications administered during the first week of inpatient treatment

As noted in **Section 2.2.11.1 above**, the standard protocol for the treatment of amphetamine withdrawal symptoms used at the clinic where this study was conducted included a range of medications, all of which were administered on an 'as needed' or prn basis. Almost two-thirds (65%) of the subjects (13/20) received the antipsychotic medication, pericyazine (for control of agitation) during the first week of abstinence from amphetamines (mean = 4.5, SEM = 0.60 mg per day). Of the specific withdrawal symptoms measured in this study, only agitation ($r = 0.31$, $p < 0.01$), poor concentration ($r = 0.29$, $p < 0.01$) and suicidal ideation ($r = 0.34$, $p < 0.01$) were significantly related to pericyazine dosage in those who received this medication.

All benzodiazepines administered (hypnotics and anxiolytics) were converted into diazepam equivalents (Ciraulo & Greenblatt, 1995) to provide a single continuous variable for analysis. Benzodiazepines (mean = 15.5, SEM = 1.45 mg per day) were administered to 13/20 (65%) subjects during the study period. Sedation was administered to 6/20 (30%) of the subjects and 10/20 (50%) received some form of analgesia during the first week of abstinence.

Total hours of sleep ($r = 0.22$, $p < 0.05$) and night sleep ($r = 0.28$, $p < 0.01$) correlated modestly with benzodiazepine dosage while a weak negative correlation between sleep latency and benzodiazepine dosage was identified ($r = -0.26$, $p < 0.05$). Of the specific withdrawal symptoms measured in this study, only agitation ($r = 0.26$, $p < 0.05$) was weakly but significantly related to benzodiazepine dosage. There was a moderately strong positive relationship between the amount of benzodiazepines and pericyazine administered during the first week of abstinence ($r = 0.60$, $p < 0.01$).

2.3.16. Predictors of withdrawal severity

Using the aggregate AWQ score as the dependent variable, linear regression analysis was performed to identify predictors of withdrawal severity during the first week of abstinence. Preliminary bivariate correlational analysis was performed to identify independent variables. Potential predictors were identified based on the strength of their correlation ($>.30$) with the dependent variable. Using the standard method, three continuous variables were entered into the regression model: age at which regular use of amphetamines commenced, intensity of amphetamine use in the previous month[2] and the severity of amphetamine dependence (SDS). The model was significant ($F = 22.96$, df 3,81 $p < 0.001$), explaining 46% of the variance in withdrawal scores (adjusted $R^2 = 0.44$). Multicollinearity was satisfactory; the highest correlation between independent variables was $r = 0.28$ between the amount of amphetamines used in the previous month and the SDS. All three independent variables were significant predictors of withdrawal severity: age at which regular use of amphetamines began ($\beta = -0.32$, $p < 0.001$), indicating that younger age of starting regular amphetamine use was associated with increased withdrawal severity; intensity of amphetamine use in the previous month ($\beta = 0.39$, $p < 0.001$), indicating that the greater the amount of amphetamine use, the more severe the abstinence syndrome and SDS ($\beta = 0.36$, $p = 0.001$),

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[2] Intensity of amphetamine use was measured using a summary variable that multiplied the number of days used by the number of times used per day in the previous month.

indicating that greater dependence on amphetamine was associated with a more severe withdrawal course.

2.4.   Discussion

This study confirmed clinical reports of a withdrawal syndrome on cessation of amphetamine use in dependant users. For the present sample, 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. Those subjects who had been using amphetamines longer, were more dependent and who had been using greater amounts of amphetamines in the month prior to admission for treatment experienced a more severe withdrawal course.

Craving for amphetamine was consistently high over the different measures used. Craving 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, loss of interest or pleasure (anhedonia), oversleeping (hypersomnia), tension, agitation and inactivity remained moderate to severe and did not decline during the study period. 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. It is possible that anxiety and irritability are features of a prolonged withdrawal syndrome.

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. It is possible however, that subject's mood may have shown further changes given a longer study period. Symptoms such as increased appetite, motor retardation and difficulty concentrating were all moderately elevated, remaining 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.

Clinical reports of a 'crash' period characterised by relative oversleeping for around three days following the last use of amphetamine were supported by our

results. Sleep characteristics such as clearheadedness on arising, depth, quality and satisfaction with night sleep improved rapidly following admission, remaining stable and at moderate levels for the subsequent seven nights of inpatient treatment. The increase in total hours of sleep between pre-admission and the peak at day two when subjects slept for around 14 hours was striking. However, following this peak, hours of sleep gradually declined, although remaining at around eight hours per night. It is possible that given a longer data collection period, hours of sleep would have continued to decline as shown in a previous study of newly abstinent amphetamine users (Gossop *et al.*, 1982). In their investigation, Gossop and colleagues showed that hospitalised amphetamine users slept significantly less than did comparison subjects over the total study period of 20 days. The comparative reduction in sleep was particularly marked in the later phase of the study (days 6 – 20). While insomnia (as measured by a single item on the ASSA) was severe prior to admission, there was a rapid improvement following admission for treatment. Interestingly, subjects had steadily increasing levels of vivid, unpleasant dreams throughout the study period. These vivid dreams may have been a function of rebound REM sleep following a period of sleep deprivation (Gillin, Pulvirenti, Withers, Golshan & Koob, 1994).

In common with other samples of amphetamine users (Hawks *et al.*, 1969), reduced hours of sleep were reported in the week prior to interview. The median number of hours of sleep in the seven days prior to admission to the inpatient clinic was around half of what would be expected in normal, healthy adults; that is, around eight hours of sleep per night (Carskadon & Dement, 1994). This pre-admission hyposomnia probably reflects the stimulant properties of amphetamine used in that time period. Importantly, there was no relationship between the number of hours of sleep in the week prior to admission and hours of sleep during the first week of abstinence. This finding is consistent with that of Angrist and Sudilovsky (1978) who noted that even where patients had sufficient sleep, they still experienced several days of fatigue in the early phase of abstinence. Therefore, the oversleeping characteristic of the early period of amphetamine withdrawal does not seem to be simply a function of the degree of sleep deprivation prior to admission for treatment.

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 alcohol (White *et al.*, 1994) or opioid withdrawal (Handelsman *et al.*, 1987), there were no directly measurable amphetamine withdrawal signs. Objective measures such as pulse and blood pressure remained within normal limits for the duration of the study period. However, the positive relationship between subjective withdrawal symptoms and the observer-rated evaluation of withdrawal severity indicated that experienced clinicians are able to provide a reasonably accurate and consistent judgement as to the current level of discomfort experienced by patients in amphetamine withdrawal. Additionally, the number of hours of sleep provides an observable indication of the time course and severity of withdrawal.

2.4.1. Limitations of the study

An important issue in interpreting the results of this study is the use of psychoactive medication to ameliorate withdrawal symptoms. Use of medication may have masked some withdrawal symptoms, particularly insomnia. The absence of a control group and the use of self-report measures to assess sleep were further limitations as was the brief time period over which the subjects were studied. It is possible that eight days may not have been long enough for some symptoms to change or to emerge. 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.

2.4.2. Summary and conclusions

This study clearly defined an amphetamine withdrawal syndrome characterised principally by dysphoria, fatigue, irritability, anxiety and vivid, unpleasant dreams. While insomnia showed a statistically significant change, the marked reduction over the first 24 hours of abstinence probably reflected an initial residual stimulant effect that rapidly disappeared rather than the emergence of a withdrawal symptom. Withdrawal severity increased markedly within the first 24 hours following the last use of amphetamines before reaching a peak between 48 and 72

hours following the last use. Symptom severity had declined by the fourth day, and continued to do so for the remainder of the first week of abstinence. The time course of amphetamine withdrawal syndrome identified in this study was consistent with clinical reports of a peak at around 2 – 4 days of abstinence (Lago & Kosten, 1994). Additionally, the finding that duration and intensity of amphetamine use was associated with a more severe withdrawal syndrome is consistent with theories that withdrawal symptoms may, to some extent, represent a 'rebound' phenomenon (West & Gossop, 1994).

3.   CHAPTER 3: AMPHETAMINE WITHDRAWAL STUDY, THAILAND

3.1.   Introduction

As noted in the previous chapter, high levels of illicit amphetamine use have occurred in both Australia (Topp *et al.*, 2002; Australian Illicit Drug Report, 2003) and Thailand (Cheurprakobkit, 2000; National Household Survey Thailand, 2001; Bureau for International Narcotics and Law Enforcement Affairs, 2002; Ahmad, 2003). Thailand has faced a threefold illicit drug problem in that it has been a producer, consumer and exporter of illicit drugs (mostly opioids). However, as efforts to reduce the production, consumption and export of heroin and opium have shown success, production of amphetamines has increased as opioid manufacturers diversify into the production of amphetamines to maintain profits (Cheurprakobkit, 2000; Humeniuk & Ali, 2004).

Much of this illicit amphetamine production is thought to occur in clandestine laboratories along the Thai-Myanmar border and in the Yunnan Province in Southern China (Farrell & Marsden, 2002). Consequently, there has been a substantial increase in methamphetamine use in Thailand, particularly in those Northern provinces close to the presumed sites of illicit methamphetamine production. For example, a recent survey in Chiang Rai Province, Northern Thailand, found a high prevalence of methamphetamine use among young people. Results of this survey showed that 41% of male and 19% of female students in three vocational (post-secondary) schools had used methamphetamine (Sattah, Supawitkul, Dondero, Kilmarx, Young, Mastro, Chaikummao, Manopaiboon & Griensven, 2002).

Increased use of methamphetamine in Thailand and the subsequent harms to the individual and the community have resulted in increased demand for amphetamine dependence treatment (Verachai, Dechongkit, Patarakorn & Lukanapichonchut, 2001; Farrell & Marsden, 2002; Melbye, Khamboonruang, Kunawararak, Celentano, Prapamontol, Nelson, Natpratan & Beyrer, 2002; Sattah *et al.*, 2002; Ahmad, 2003; Srisurapanont *et al.*, 2003; Humeniuk & Ali, 2004). Given the increase in demand, it becomes important to offer effective treatments based on an empirically-based understanding of the likely time course and severity of

withdrawal symptoms. Experience with the general treatment of drug dependence has shown that effective treatments can have a significant impact on the health and well-being of illicit drug users (Gowing *et al.*, 2001).

As outlined in the previous chapter, a pattern of amphetamine withdrawal symptoms was identified over the first week of abstinence in a sample of Australian amphetamine-dependent inpatients. In the previously described study, withdrawal symptoms increased markedly over the first 24 – 48 hours of abstinence, peaking at between 48 and 72 hours from the final amphetamine use. The withdrawal syndrome identified in the Australian study was characterised principally by subjective measures of depression, vivid dreams and fatigue, all of which changed significantly during the first week of abstinence. Levels of discomfort had declined by the fourth day, and continued to decrease until the end of the first week of abstinence when data collection ceased (see **Chapter 2**). However, clinical reports and some studies have indicated that symptoms of withdrawal may persist for several weeks or months following cessation of regular use (Watson *et al.*, 1972; Gossop *et al.*, 1982; Hofmann, 1983). Therefore, assessment of amphetamine withdrawal over a longer period would provide a more complete depiction of the syndrome.

To provide data on withdrawal symptoms experienced over a greater time period than that assessed in the Australian study (described in **Chapter 2**) a second study was designed using similar methodology but covering the first three weeks of abstinence. The second withdrawal study was conducted in Thailand.

3.1.1. Thailand withdrawal study: aims

The aims of the second withdrawal study were to identify and measure symptoms arising in the first three weeks of abstinence in a sample of amphetamine-dependent inpatients. Specifically, to:

i)   quantify the severity of amphetamine withdrawal symptoms during the first three weeks of abstinence

ii) describe the time course of amphetamine withdrawal symptoms during the first three weeks of abstinence

3.2. Method

3.2.1. Study design

Cross sectional, comparison group design

3.2.2. Study setting

The study was conducted at the Northern Drug Dependence Treatment Centre (NDDTC), the major treatment facility for substance dependence in the region. Located in Chiang Mai Province, Thailand, the NDDTC treats a large number of licit and illicit drug users annually. The centre services a large area in the north of the country, offering withdrawal and rehabilitation services for a range of illicit and licit drug problems. As well as providing treatment services, the centre also has a strong research presence internationally having been involved in collaborative trials with organisations in other countries including Australia, the United Kingdom and the United States.

3.2.3. Training

Prior to the commencement of the study, a training workshop involving key members of NDDTC clinical staff was conducted by the study investigators (Manit Srisurapanont, Jason White and Catherine McGregor). Subsequently, smaller workshops were conducted with nursing staff to ensure that they were familiar with the study protocol and instruments. Individual training sessions were held with those staff who could not attend the workshops due to rostering issues. All workshop training materials, instruments and study protocols were translated into Thai.

3.2.4. Timeframe of data collection

Data collection took place between October 2002 and February 2003.

3.2.5. Ethical considerations

This study received ethics approval from both the Ethical Review Committee for Research on Human Subjects, Ministry of Public Health in Thailand and the University of Adelaide Human Research Ethics Committee.

3.2.6.   Sample size

Sample size for the present study was based on two studies that have assessed withdrawal symptoms in regular amphetamine users over time. The first study, a systematic study of sleeping patterns in amphetamine users undergoing inpatient withdrawal, found significant differences between experimental and control groups in hours of sleep among 20 inpatients being treated for amphetamine withdrawal (Gossop *et al.*, 1982). The second study examined a range of symptoms over three time points during amineptine treatment for withdrawal symptoms in two groups of amphetamine users. In comparison to controls ($n = 22$), the amineptine group ($n = 21$) showed significant reductions in three symptoms, fatigue, increased appetite and increased sleep at the end of the first and second week of treatment (Srisurapanont *et al.*, 1999). Based on these previous studies, a sample size of 21 is expected to provide adequate power to map the nature, time course and severity of amphetamine withdrawal.

3.2.7.   Study subjects

Consecutive admissions to NDDTC for amphetamine withdrawal treatment were assessed for consistency with the selection criteria. Patients were screened for participation in the study following the completion of the standard clinic nursing and medical admission process and following consultation with the clinical staff. That is, participants were only approached once they had undergone the standard clinic admission. There was no reimbursement for study participation.

3.2.8.   Study criteria

Individuals admitted to NDDTC, Chiang Mai, Thailand for treatment of amphetamine dependence and fulfilling the following criteria:

3.2.8.1.   Inclusion criteria

3.2.8.1.1.   Aged 18 – 45 years

3.2.8.1.2.   Urine sample positive for amphetamines

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

3.2.8.2. Exclusion criteria

3.2.8.2.1. Currently prescribed medication for cardiovascular disease, central nervous system disease, liver disease or kidney disease

3.2.8.2.2. Allergic reaction to benzodiazepines

3.2.8.2.3. Concurrent acute medical or psychiatric illness requiring psychotropic medication or acute care hospitalisation

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

3.2.8.2.5. Fulfils the DSM-IV diagnostic criteria for other substance dependence, except nicotine

3.2.8.3. Discontinuation criteria

3.2.8.3.1. Use of non-prescribed medications

3.2.8.3.2. Development of condition requiring psychotropic medications, except benzodiazepines prescribed as needed

3.2.8.3.3. Development of condition requiring treatment in an acute care medical or psychiatric institution

3.2.9. Study instruments

The same instruments and methodology were used in both Australian and Thailand withdrawal studies with the exception that the study period was extended to three weeks. All study instruments were translated into Thai prior to administration. Native Thai speakers trained in the study methodology administered all interviewer-administered questionnaires. The author (CM) supervised all data collection procedures. See **Section 2.2.8 above**, for a full description of study instruments.

3.2.9.1.   Instruments administered on admission

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

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

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

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

3.2.9.2.   Instruments administered daily during the first three weeks of abstinence

The following instruments were administered once per day during the first three weeks of abstinence.

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

3.2.9.2.2.   Modified version of the Cocaine Selective Severity Assessment scale (ASSA) (Kampman *et al.*, 1998)

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

Subjects were also asked to provide an estimation of the total number of hours of sleep in the week prior to admission for comparison with sleep variables in the first week of abstinence.

3.2.9.2.4.   Modified version of the Cocaine Craving Questionnaire (ACQ) (Tiffany *et al.*, 1993)

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

Nursing staff also recorded the radial pulse and blood pressure daily for each subject. Copies of translated study instruments are included in **Appendix 2**.

3.2.10. Data collection and collation

At the time of data collection, the usual length of stay in the inpatient unit for medical treatment of acute amphetamine withdrawal was 21 days. Therefore, data were collected for up to the first three weeks of abstinence. Questionnaires (i.e. ASSA, AWQ, ACQ, 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 21 (days 0 – 20).

3.2.11. 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. For normally distributed continuous variables *t*-tests were employed. Where distributions were highly skewed, medians were reported and data analysed using the Mann-Whitney *U* test. Predictors of continuous variables such as withdrawal severity were identified by linear regression analysis. Pearson's product-moment correlation coefficient was reported for 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.

3.2.12. Procedure

This study incorporated the standard protocol currently used for the screening and admission of NDDTC clients. No subject was mandated for treatment and almost all were referred by a family member. Clients were admitted for treatment through the clinic Outpatient Department as per the usual clinic protocol. On presentation to NDDTC they were interviewed by outpatient nursing staff. This initial interview

comprised an extensive history including drug use history, drug treatment and withdrawal history, medical and psychiatric history and a psychosocial history.

Following the initial admission process, clients underwent a medical examination by the clinic medical officer. Clients were required by the clinic to provide a sample of urine for drug screening following which they were transferred to the amphetamine ward where there were interviewed by a member of the ward nursing staff. If no exclusion criteria had become evident as a result of the nursing admission process and medical examination, the client's name was flagged as a potential study subject. At this point, the potential subject was given a verbal explanation of the study protocol by the ward nurse together with the study information sheet and consent form (translated into Thai). If the potential subject expressed an interest in joining the study, informed consent to participate was obtained. Study enrolment was confirmed where the admission urine test report identified the recent use of amphetamines.

All data collection instruments were administered by native Thai speakers under the supervision of the author (CM), or supervised by the author in the case of self-report measures. Subjects gave written informed consent prior to the commencement of data collection. Subjects in the study, in common with other clients, received the supportive counselling, group work and occupational therapy that is a standard part of inpatient treatment for amphetamine dependence at NDDTC.

3.2.13. Medication administered during the first three weeks of abstinence

All subjects received an oral B-complex vitamin capsule daily. Of the 21 subjects enrolled in the study, two received 5mg of diazepam on one occasion and one received 10mg of diazepam on one occasion for insomnia.

Once informed consent was obtained, substance dependence was assessed using the DSM-IV criteria. Providing the client was identified as being dependent on amphetamines and/or nicotine only, the structured interview schedule assessing drug use and treatment history was administered. Thereafter, each subject completed four questionnaires daily (including the day of admission): three

questionnaires assessing the nature and severity of withdrawal symptoms and craving, and one assessing sleep. In addition, a member of the clinical staff provided an observer-rated measure of withdrawal symptoms daily in respect of each subject.

3.2.14. Urine drug screens

Urine drug screens were conducted on study admission to confirm recent use, then at weekly intervals thereafter to confirm abstinence from amphetamine. Urine was analysed by Cloned Enzyme Donor Immunoassay using a cut off level of 1,000 ng/mL.

3.2.15. Comparison group

To provide comparison data, a group of nine age and sex matched (non-dependent) healthy individuals from the same geographical area completed the same withdrawal and sleep questionnaires over the same time period. Five comparison group members were recruited from among staff at the clinic (e.g., security staff, clerical officers). The remaining four were medical students studying at Chiang Mai University. Suitable comparison group members were approached individually by a member of the research team and invited to participate. There were no refusals and no compensation was offered for study participation.

3.3. Results

Of 72 patients who were admitted for treatment of amphetamine dependence during the study period, three declined to participate, 11 were currently experiencing auditory hallucinations requiring treatment with anti-psychotic medication, eight had concurrent dependence on alcohol, 14 were under 18 years of age and 15 provided a urine sample negative for amphetamines.

The final sample comprised 21 inpatient subjects, five of whom provided data on Day 0; 12 on Day 1; 18 on Days 2 and 3; 19 on Days 4 – 9; 18 on Days 10 – 14; 16 on Days 15 – 17 and 15 on days 18 – 20.

3.3.1. Sample characteristics

Table 3.1 shows the characteristics of the study sample. Only one female participated in the study and few had a partner at the time of entering treatment. The majority of subjects had completed secondary education and were currently unemployed. For all inpatient subjects, amphetamines were administered by heating methamphetamine tablets (usually on a piece of foil) and then inhaling the fumes. All subjects reported using amphetamines daily in the month prior to treatment entry.

Table 3.1   *Characteristics of the study sample*

Characteristics	(*n* = 21)
Age; mean years (range)	21.4 (18 – 28)
Male *n* (%)	20 (95)
Unemployed *n* (%)	16 (76)
Unmarried *n* (%)	20 (95)
Education	
Secondary *n (%)*	14 (67)
Vocational/Trade School *n (%)*	6 (29)
University *n (%)*	1 (5)
Age first used amphetamine; mean years (range)	17 (11 – 25)
Length of regular amphetamine use; mean years (range)	4 (1 – 15)
Amount (tablets) used per day in the previous month, median (range)	2.5 (1 – 8)
Amount (Thai Baht*) spent per day on amphetamines, median (range)	200 (70.00 – 850.0)
Previous treatment for amphetamine dependence, *n* (%)	6 (29)
Severity of Dependence Scale, mean (range)	6.2 (2 – 11)

* At the time of the study exchanges rates were Thai Baht 42.44 = US$1 and Thai Baht 41.82 = €1

3.3.2. Treatment retention

The mean number of days on which inpatient subjects remained in the study was 17.9 (SEM = 1.7) range: 3 – 21 days. Of the 21 inpatients enrolled in the study, four left the clinic prior to completing treatment, two developed auditory

hallucinations requiring acute treatment and were withdrawn from the study, and 15 completed amphetamine withdrawal treatment.

3.3.3. Depression

On average, admission BDI scores fell into the moderate category (mean = 23.6, SEM = 2.2). At the beginning of weeks two (mean = 12.1, SEM = 3.0) and three of inpatient treatment (mean = 9.8, SEM = 3.0) BDI scores had reduced on average to the minimal depression category. This reduction in BDI scores over the first three weeks of abstinence was significant (F = 7.6, df 2,54 p < 0.01). **Table 3.2** shows the BDI depression severity groupings during the study period.

Table 3.2 **BDI depression severity groupings over the first three weeks of abstinence**

	BDI severity groupings			
Time	**0 – 13 Minimal %**	**14 – 19 Mild %**	**20 – 28 Moderate %**	**29 – 63 Severe %**
Admission	14	14	48	24
Week Two	68	0	16	16
Week Three	64	12	12	12

On admission, 14% of patients each fell into the minimal and mild depression categories while 48% and 24% fell into the moderate and severe categories respectively. By the beginning of the third week of abstinence, almost two-thirds (64%) had minimal depression while 12% each fell into the mild, moderate and severe BDI depression categories.

### 3.3.4. Measurement of the time course and severity of withdrawal

The following section describes the time course and severity of withdrawal phenomena measured by the three withdrawal instruments used in this study – the self-completed Amphetamine Withdrawal Questionnaire (AWQ), the interviewer-

administered Amphetamine Selective Severity Assessment (ASSA) and the observer-rated Clinical Global Impressions scale (CGI).

### 3.3.4.1.   *Time course of withdrawal symptoms: aggregate AWQ scores*

Figure 3.1 shows the pattern of withdrawal symptoms measured by the AWQ. Withdrawal severity reduced significantly over the 21 day study time period ($F = 3.5$, df 20,475 $p < 0.001$). There was a significant difference between subjects and controls ($F = 144.6$, df 1,475 $p < 0.001$) and a significant interaction effect of time and group ($F = 2.4$, df 20,475 $p < 0.003$).

Figure 3.1   Time course of withdrawal symptoms: aggregate AWQ scores
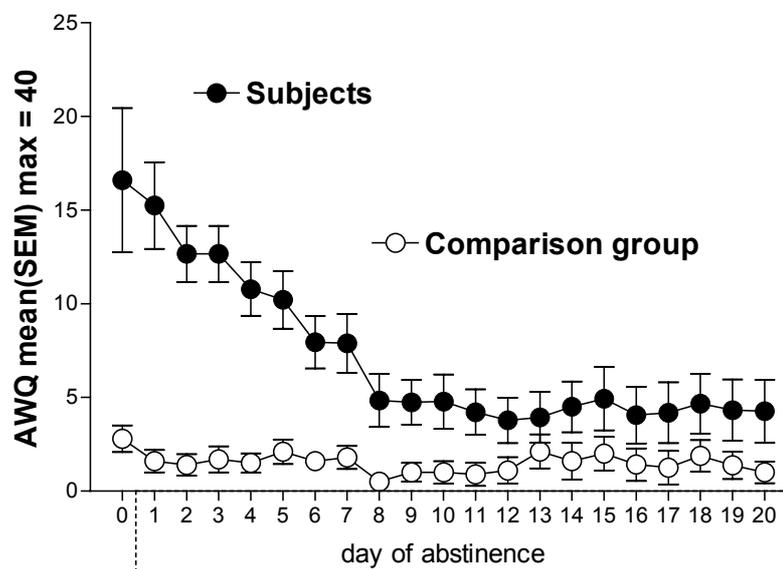
3.3.4.2.   *Time course of craving and anxiety-related symptoms (AWQ)*

Figure 3.2 shows the time course of four of the AWQ items. There was a significant difference ($F = 34.0$, df 1,475 $p < 0.001$) between groups for anxiety (see **Figure 3.2: Panel 1**); and a significant effect for time ($F = 1.9$, df 20,475 $p < 0.01$) and group ($F = 34.0$, df 1,475 $p < 0.001$) for agitation (see **Figure 3.2: Panel 2**). For amphetamine craving intensity, there was a significant effect for time ($F = 2.1$, df 20,475 $p = 0.002$). No comparison group subject reported amphetamine craving (see **Figure 3.2: Panel 3**). There was a significant difference ($F = 25.0$, df 1,475 $p < 0.001$) between groups for vivid, unpleasant dreams (see **Figure 3.2: Panel 4**).

Figure 3.2   Time course of craving and anxiety-related symptoms (AWQ)
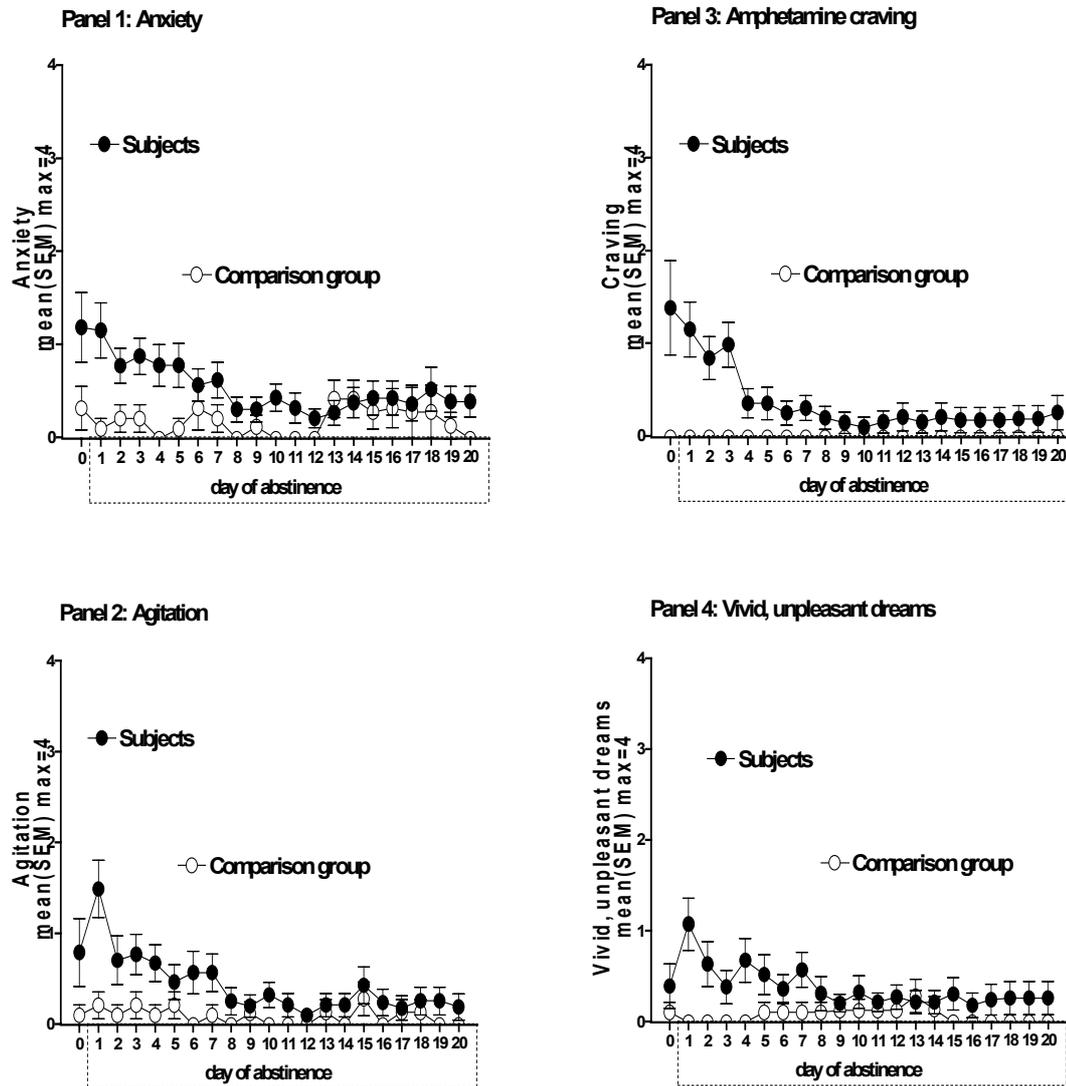
3.3.4.3.   Time course of depression-related symptoms (AWQ)

For dysphoria (see **Figure 3.3: Panel 1**), there was a significant effect of time ($F =$ 2.0, df 20,475 $p = 0.006$) and group ($F = 65.8$, df 1,475 $p < 0.001$). For motor retardation (see **Figure 3.3: Panel 2**) there was a significant time ($F = 3.0$, df 20,475 $p < 0.001$) group ($F = 63.59$, df 1,475 $p < 0.001$) and interaction effect ($F = 2.4$, df 20,475 $p < 0.001$). Similarly, for anhedonia (see **Figure 3.3: Panel 3**) there was a significant time ($F = 2.0$, df 20,475 $p < 0.001$), group ($F = 65.8$, df 1,475 $p <$ 0.001) and interaction effect ($F = 1.7$, df 20,475 $p = 0.029$). For fatigue (see **Figure**

3.3: Panel 4) there was a significant time (F = 4.9, df 20,475 p < 0.001), group (F = 89.0, df 1,475 p < 0.001) and interaction effect (F = 3.1, df 20,475 p < 0.001).

Figure 3.3   Time course of depression-related symptoms (AWQ)
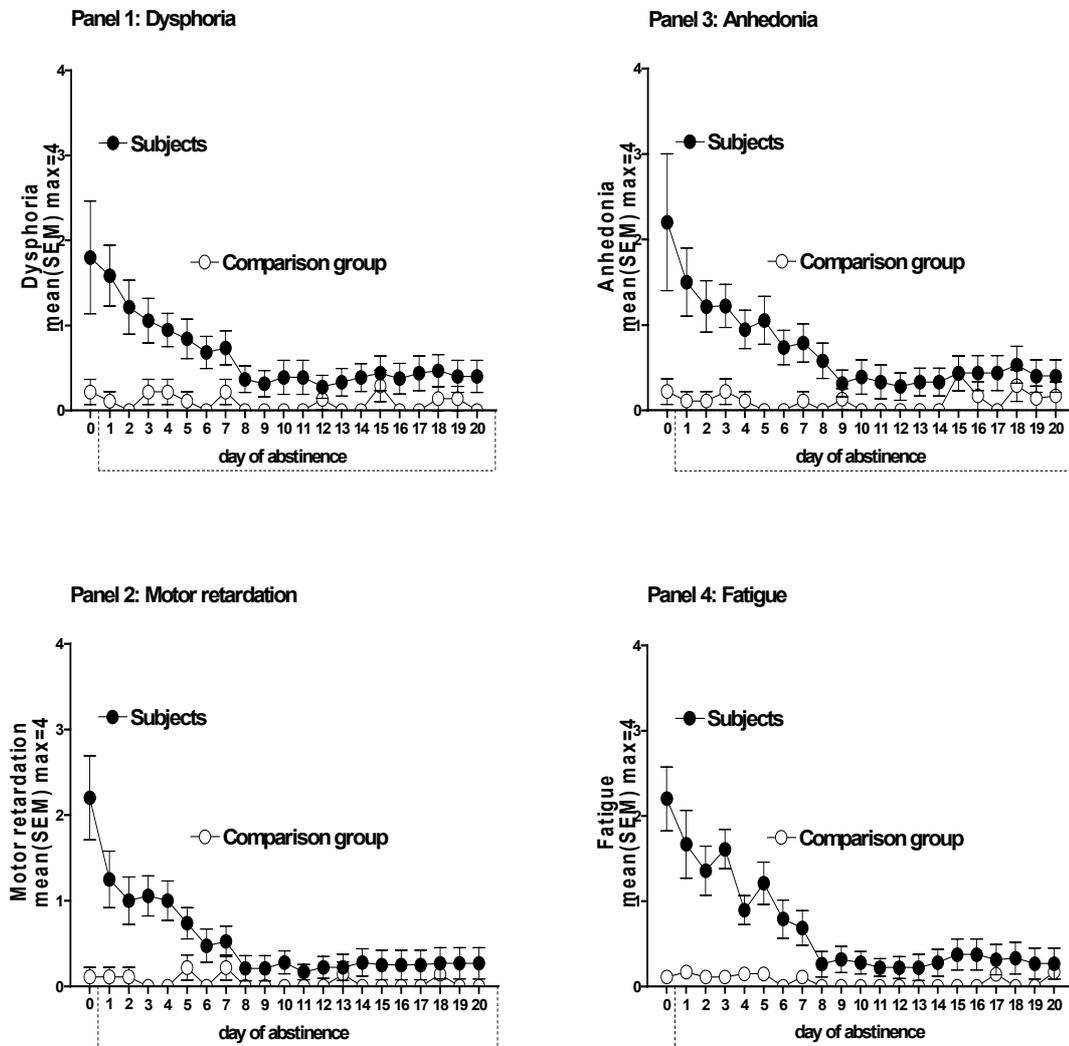
3.3.4.4.   Time course of appetite and sleep-related symptoms (AWQ)

There was a significant group effect (F = 149.7, df 1,475 p < 0.001) for increased appetite (see **Figure 3.4: Panel 1**), while for increased sleep (see **Figure 3.4: Panel 2**) there was a significant time (F = 3.1, df 20,475 p < 0.001) group (F = 130.8, df 1,475 p < 0.001) and interaction effect (F = 2.3, df 20,475 p < 0.001).

Figure 3.4   Time course of appetite and sleep-related symptoms (AWQ)

Panel 1: Increased appetite

Panel 2: Increased sleep
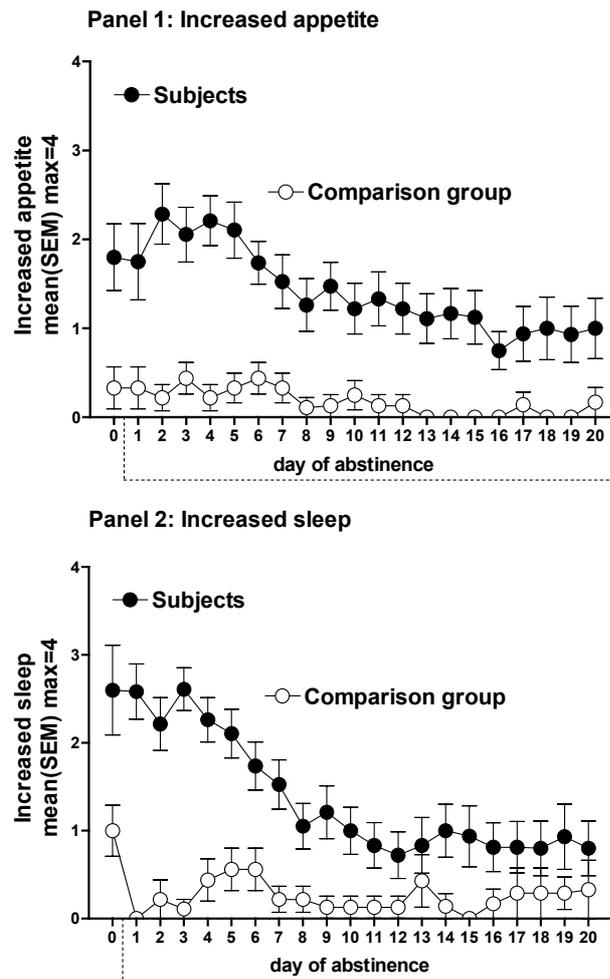
3.3.4.5.   Severity of amphetamine withdrawal symptoms (AWQ items)

Table 3.3 details the mean and SEM associated with each item score together with the *p* value of change over the first three weeks of amphetamine abstinence. All ten of the AWQ items changed significantly over the study period. Of the symptoms measured by the AWQ, appetite and sleep-related symptoms were the most severe followed by depression-related symptoms such as anhedonia, fatigue and dysphoria. Anxiety, motor retardation, agitation and vivid dreams were less marked symptoms, while craving intensity was the least severe withdrawal symptom.

Table 3.3   *Severity of amphetamine withdrawal symptoms (AWQ items)*

AWQ item	Mean	SEM	*p*
Increased appetite	1.42	0.07	*0.001*
Increased sleep	1.38	0.07	*0.001*
Anhedonia	0.65	0.05	*0.001*
Fatigue	0.62	0.05	*0.001*
Dysphoria	0.60	0.04	*0.001*
Anxiety	0.53	0.04	*0.001*
Motor retardation	0.48	0.04	*0.001*
Agitation	0.42	0.04	*0.001*
Vivid, unpleasant dreams	0.36	0.04	*0.001*
Craving intensity	0.35	0.04	*0.001*

3.3.4.6.   *Predictors of withdrawal severity as measured by the AWQ*

Using the aggregate AWQ score as the dependent variable, linear regression analysis was performed to identify predictors of withdrawal severity during the first three weeks of abstinence. Using the standard method, three continuous variables were entered into the regression model: age, length of amphetamine use and number of DSM-IV amphetamine dependence criteria met. Although the model was significant ($F = 29$, df 3,346 $p < 0.001$), only 21% of the variance in withdrawal scores was predicted. Multicollinearity was satisfactory: the highest correlation between independent variables was $r = 0.27$ between age and DSM-IV criteria. The correlation between age and length of amphetamine use was surprisingly low at $r = -0.13$. All three independent variables were significant positive predictors of withdrawal severity: years of age ($\beta = 0.33$, $p < 0.001$), years of amphetamine use ($\beta = 0.27$, $p < 0.001$) and number of DSM-IV amphetamine dependence criteria met ($\beta = 0.11$, $p = 0.03$).

3.3.4.7. Time course of withdrawal symptoms: aggregate ASSA scores

Figure 3.5 shows the time course of withdrawal discomfort as measured by aggregate ASSA scores over the 21 day study time period. There was a significant effect for time (F = 5.7, df 20,476 p < 0.001) and group (F = 117.6, df 1,476 p < 0.001) and a significant interaction effect of time and group (F = 3.8, df 20,476 p < 0.001).

*Figure 3.5   Time course of withdrawal symptoms: aggregate ASSA scores*
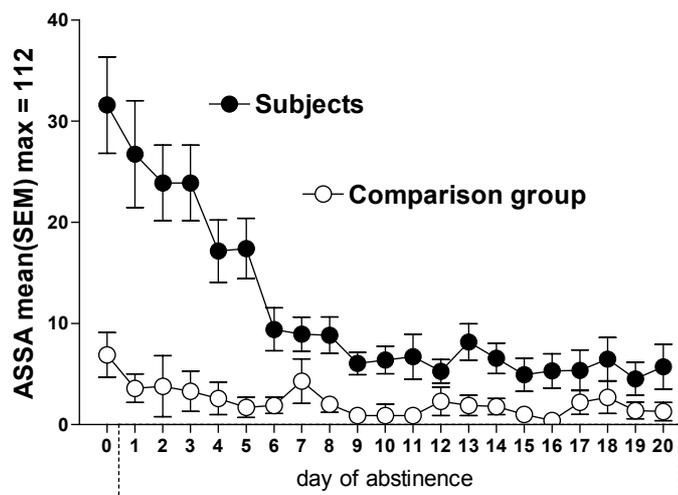
Reliability analysis (Cronbach's alpha) of the modified CSSA showed satisfactory internal consistency (0.80) that compared favourably with reliability analysis for the AWQ (0.90).

3.3.4.8. Time course of amphetamine craving, appetite and sleep-related symptoms (ASSA)

There was a significant difference between subjects and controls for hyperphagia (F = 34.0, df 1,476 p < 0.001) (see **Figure 3.6: Panel 1**) and hypophagia (F = 7.3, df 1,476 p = 0.007) (see **Figure 3.6: Panel 2**). For hypersomnia (see **Figure 3.6: Panel 3**) there was a significant effect for day of abstinence (F = 2.6, df 20,476 p < 0.001), group (F = 16.8, df 1,476 p < 0.001) and a significant interaction of day and study group (F = 2.6, df 20,476 p < 0.001). For hyposomnia, only the group difference was significant (F = 9.0, df 1,476 p = 0.003) (see **Figure 3.6: Panel 4**).

As no control subjects reported amphetamine craving, only the analysis for day of abstinence will be reported. There was a significant effect of time (F = 4.6, df 20,476 p < 0.001) for amphetamine craving intensity (see **Figure 3.6: Panel 5**) and frequency (F = 5.0, df 20,476 p < 0.001) (see **Figure 3.6: Panel 6**).
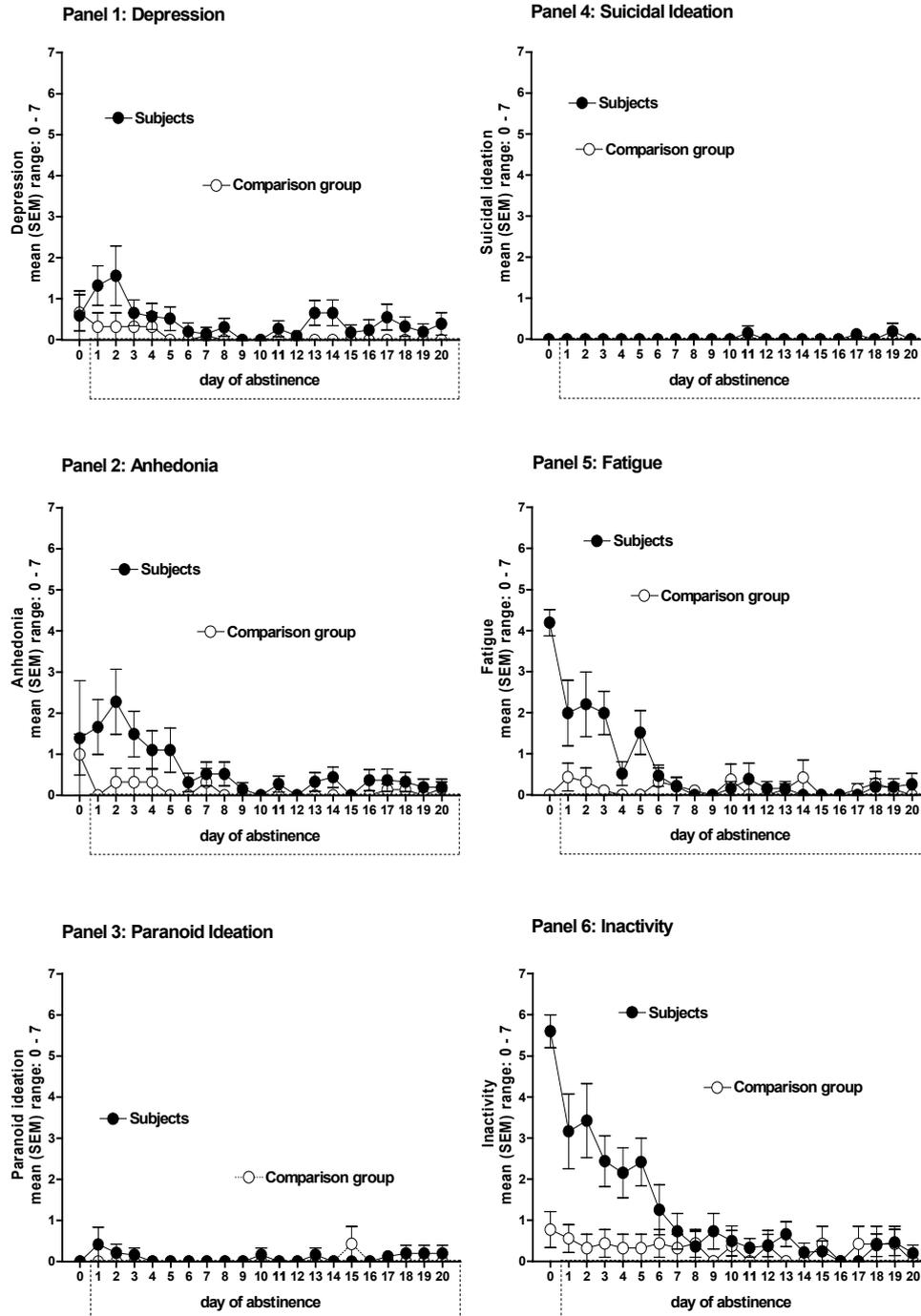
Figure 3.6   *Time course of amphetamine craving, appetite and sleep-related symptoms (ASSA)*
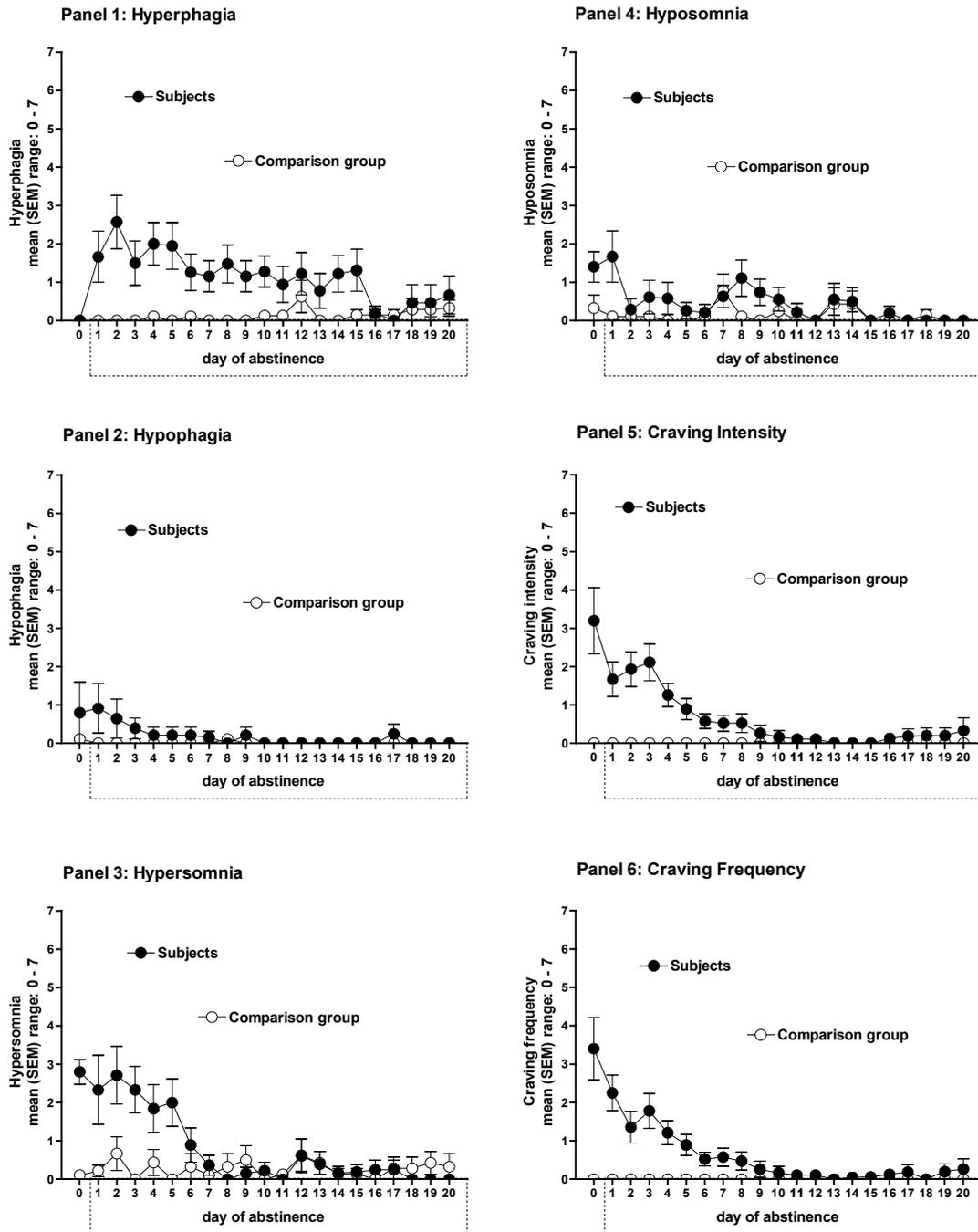
3.3.4.9. *Time course of depression-related symptoms (ASSA)*

There were significant group differences for depression ($F = 12.7$, df 1,476 $p <$ 0.001) (see **Figure 3.7: Panel 1**).

Figure 3.7   Time course of depression-related symptoms (ASSA)

For anhedonia (see **Figure 3.7: Panel 2**) there was a significant effect for time (F = 1.7, df 20,476 p = 0.038) and group (F = 15.2, df 1,476 p < 0.001). There were no significant time, group or interaction effects for paranoid ideation (see **Figure 3.7: Panel 3**) or suicidal ideation (see **Figure 3.7: Panel 4**).

There were significant time (F = 4.0, df 20,476 p < 0.001), group (F = 25.1, df 1,476 p < 0.001) and interaction effects (F = 3.8, df 20,476 p < 0.001) for fatigue (see **Figure 3.7: Panel 5**). Similarly, there were significant time (F = 3.9, df 20,476 p < 0.001), group (F = 32.0, df 1,476 p < 0.001) and interaction effects (F = 2.7, df 20,476 p < 0.001) for inactivity (see **Figure 3.7: Panel 6**).

3.3.4.10. Time course of anxiety, tension, poor concentration, irritability, craving for carbohydrates and bradycardia (ASSA)

There were significant differences between study groups for anxiety (F = 14.2, df 1,476 p < 0.001) (see **Figure 3.8: Panel 1**), but no significant time, group or interaction effects for tension (see **Figure 3.8: Panel 2**). There were significant differences between study groups for poor concentration (F = 5.6, df 1,476 p = 0.018) (see **Figure 3.8: Panel 3**). For irritability (see **Figure 3.8: Panel 4**) only time was significant (F = 1.7, df 20,476 p = 0.025).

Both time (F = 2.0, df 20,476 p = 0.007) and group (F = 81.6, df 1,476 p = < 0.001) effects were significant for carbohydrate craving (see **Figure 3.8: Panel 5**) and there were significant differences between study groups for bradycardia (F = 77.1, df 1,475 p < 0.001) (see **Figure 3.8: Panel 6**).

Figure 3.8 **Time course of anxiety, tension, poor concentration, irritability, craving for carbohydrates and bradycardia (ASSA)**
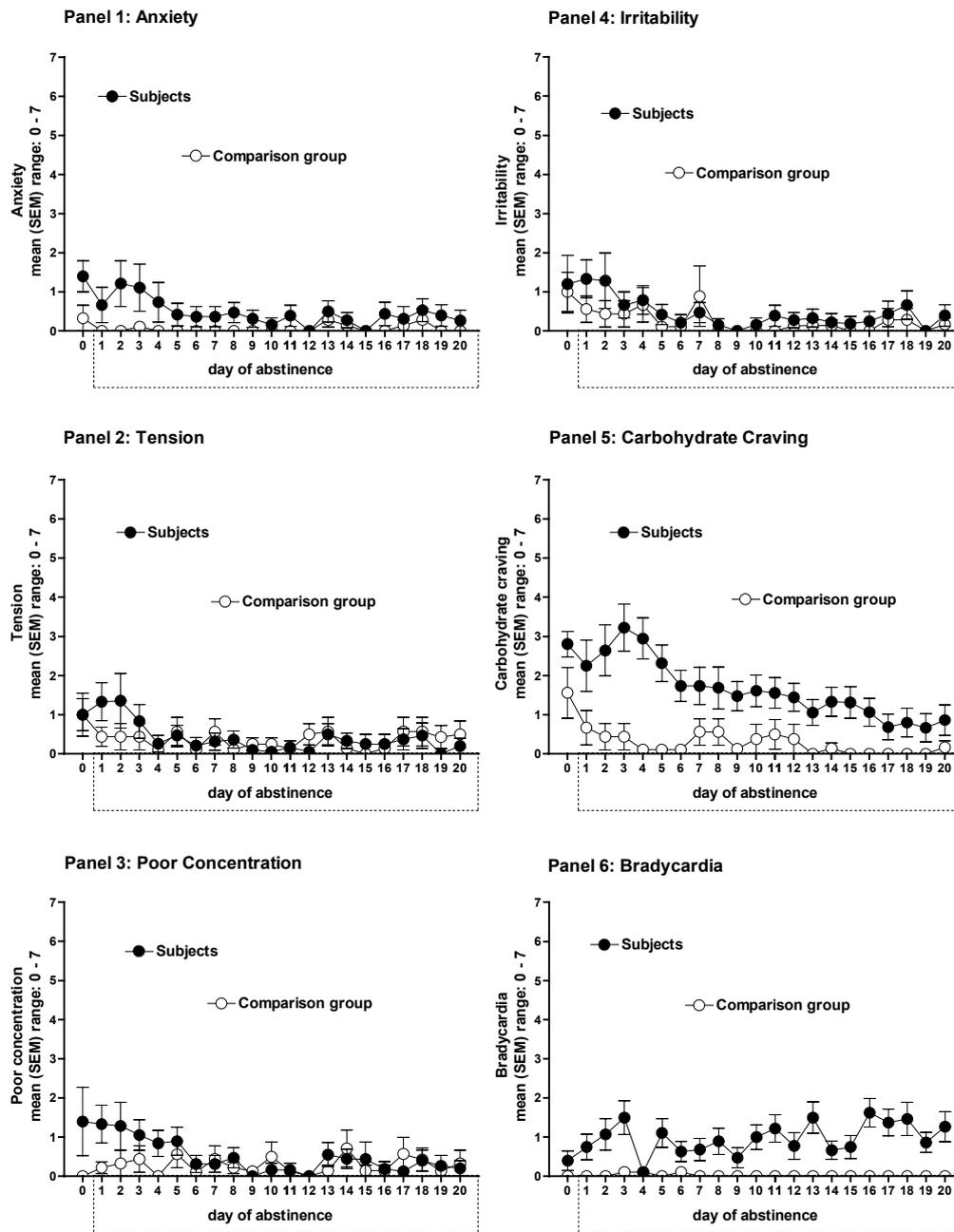
3.3.4.11. Severity of amphetamine withdrawal symptoms (ASSA items)

Severity and temporal changes in ASSA item scores were examined for the inpatient sample alone. **Table 3.4** details the mean and SEM associated with each ASSA item score together with the *p* value of change over the first three weeks of amphetamine abstinence.

Table 3.4   ***Severity of amphetamine withdrawal symptoms (ASSA items)***

ASSA Item	Mean	SEM	*p*
Carbohydrate craving	1.69	0.10	*0.001*
Hyperphagia	1.11	0.10	*0.174*
Inactivity	1.02	0.11	*0.001*
Bradycardia	0.99	0.07	*0.022*
Hypersomnia	0.74	0.10	*0.001*
Craving intensity	0.60	0.07	*0.001*
Craving frequency	0.58	0.04	*0.001*
Fatigue	0.56	0.08	*0.001*
Anhedonia	0.55	0.08	*0.001*
Tension	0.47	0.06	*0.031*
Anxiety	0.46	0.08	*0.668*
Hyposomnia	0.43	0.07	*0.008*
Irritability	0.40	0.06	*0.093*
Depression	0.39	0.06	*0.015*
Poor concentration	0.35	0.04	*0.009*
Suicidal ideation	0.35	0.04	*0.435*
Hypophagia	0.14	0.04	*0.248*
Paranoid ideation	0.02	0.01	*0.555*

Of the symptoms measured by the ASSA, craving for carbohydrates and increased appetite were the most severe followed by inactivity and bradycardia. Increased sleep and amphetamine craving as well as fatigue and anhedonia were the next most severe. Levels of paranoid ideation were low throughout the study period.

3.3.4.12. Predictors of withdrawal severity as measured by the ASSA

Using the aggregate ASSA score as the dependent variable, linear regression analysis was performed to identify predictors of withdrawal severity during the first

three weeks of abstinence. Using the standard method, four continuous variables were entered into the regression model: age, length of amphetamine use, severity of dependence (aggregate SDS score) and depression (aggregate BDI score).

Although the model was significant ($F = 9.9$, df 4,345 $p < 0.001$), only 32% of the variance in withdrawal scores was predicted. Multicollinearity was satisfactory: the highest correlation between independent variables was $r = 0.27$ between age and BDI score. All four independent variables were significant positive predictors of withdrawal severity: years of age ($\beta = 0.20$, $p = 0.0002$), years of amphetamine use ($\beta = 0.11$, $p = 0.026$), severity of dependence ($\beta = 0.10$, $p = 0.038$) and level of depression ($\beta = 0.10$, $p = 0.049$).

3.3.4.13. Vital signs

Radial pulse and blood pressure did not change significantly, staying within normal limits for the duration of the study. However, when pulse rate was changed from a continuous to a categorical variable for the ASSA scale item 'bradycardia', a significant change was revealed (see **Figure 3.8: Panel 6**).

3.3.4.14. Time course and severity of observer-rated withdrawal (CGI)

Observer-rated withdrawal (CGI) peaked on day 0 then reduced over the first eleven days of abstinence ($F = 16.9$, df 20,306 $p < 0.001$) (see **Figure 3.9**).

Figure 3.9   Time course and severity of observer-rated withdrawal (CGI)
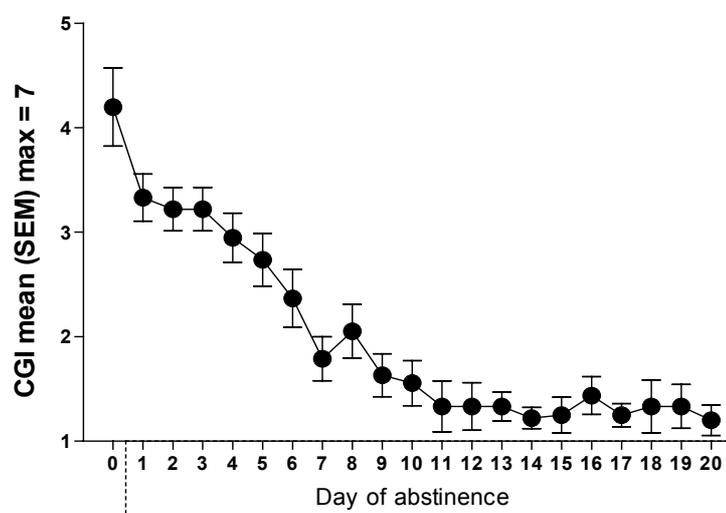
3.3.5. Amphetamine craving (ACQ)

Craving for amphetamine declined significantly over the study period (F = 4.0, df 20,306 p < 0.001, see **Figure 3.10: Panel 1**). All of the ACQ subscales changed significantly over the study period (**Figure 3.10: Panel 2**): desire to use amphetamine (F = 2.5, df 20,305 p < 0.001); planning and intention to use (F = 2.2, df 20,305 p = 0.002); anticipation of positive outcome of use (F = 3.0, df 20,306 p < 0.001); anticipation of relief from withdrawal or dysphoria (F = 3.5, df 20,306 p < 0.001) and lack of control over use (F = 3.9, df 19,291 p < 0.001).

### *Figure 3.10 Time course of craving for amphetamines (ACQ)*
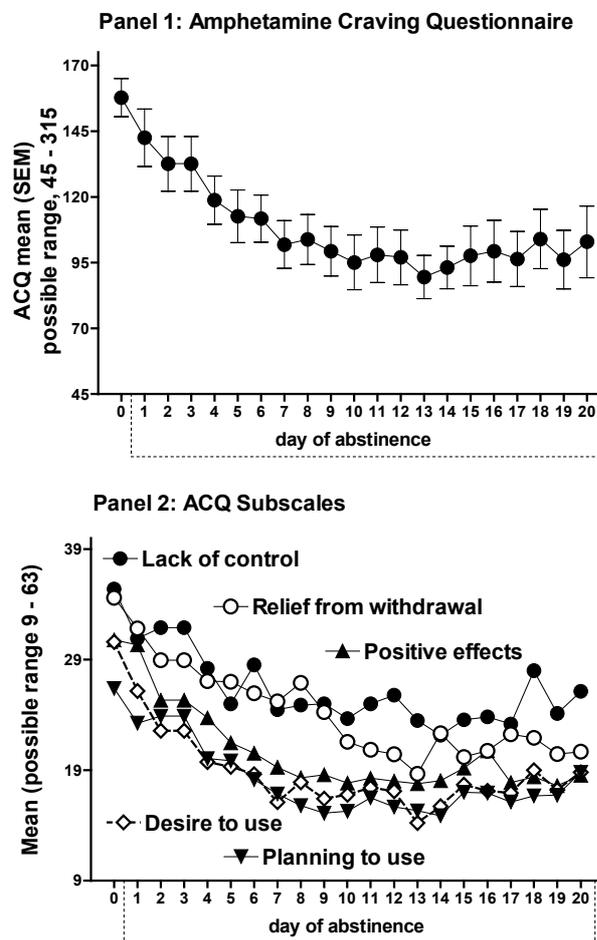
3.3.6. Sleep patterns during amphetamine withdrawal

Figure 3.11 shows the sleeping patterns (in terms of hours of sleep) among inpatients and the comparison group. There was a significant difference between

groups (F = 53.9, df 1,473 p < 0.001) for total hours of sleep (see **Figure 3.11: Panel 1**). For inpatient subjects, total hours of sleep (over the 24 hour period) changed significantly over the study period (F = 3.12, df 20,310 p < 0.001), peaking on the fifth day of abstinence.

Figure 3.11   Hours of sleep

Panel 1: Total hours of sleep

**Panel 2: Hours of daytime sleep**

Panel 3: Hours of nighttime sleep
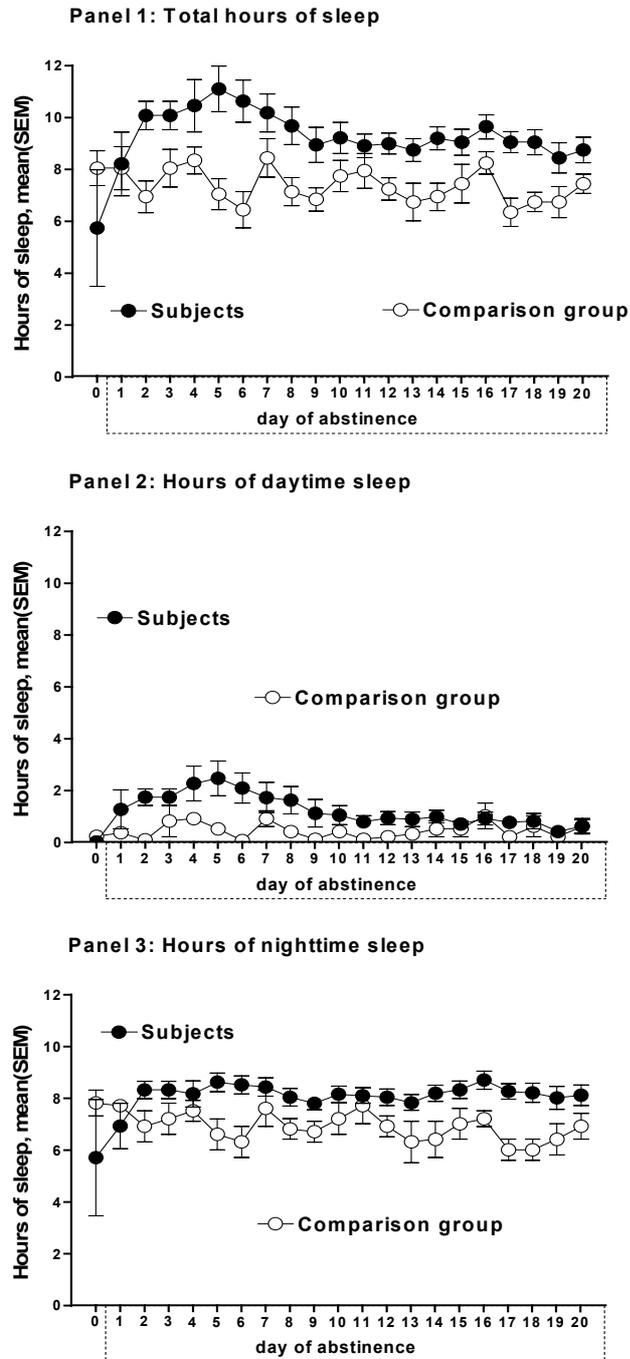
Group differences were also significant for daytime sleep (F = 24.0, df 1,473 $p <$ 0.001) (see **Figure 3.11: Panel 2**) and for night sleep (F = 41.4, df 1,473 $p <$ 0.001) (see **Figure 3.11: Panel 3**).

3.3.6.1.   *Sleep characteristics during the first three weeks of abstinence*

Sleep characteristics during amphetamine withdrawal are shown in **Figure 3.12.**

Figure 3.12   Sleep characteristics
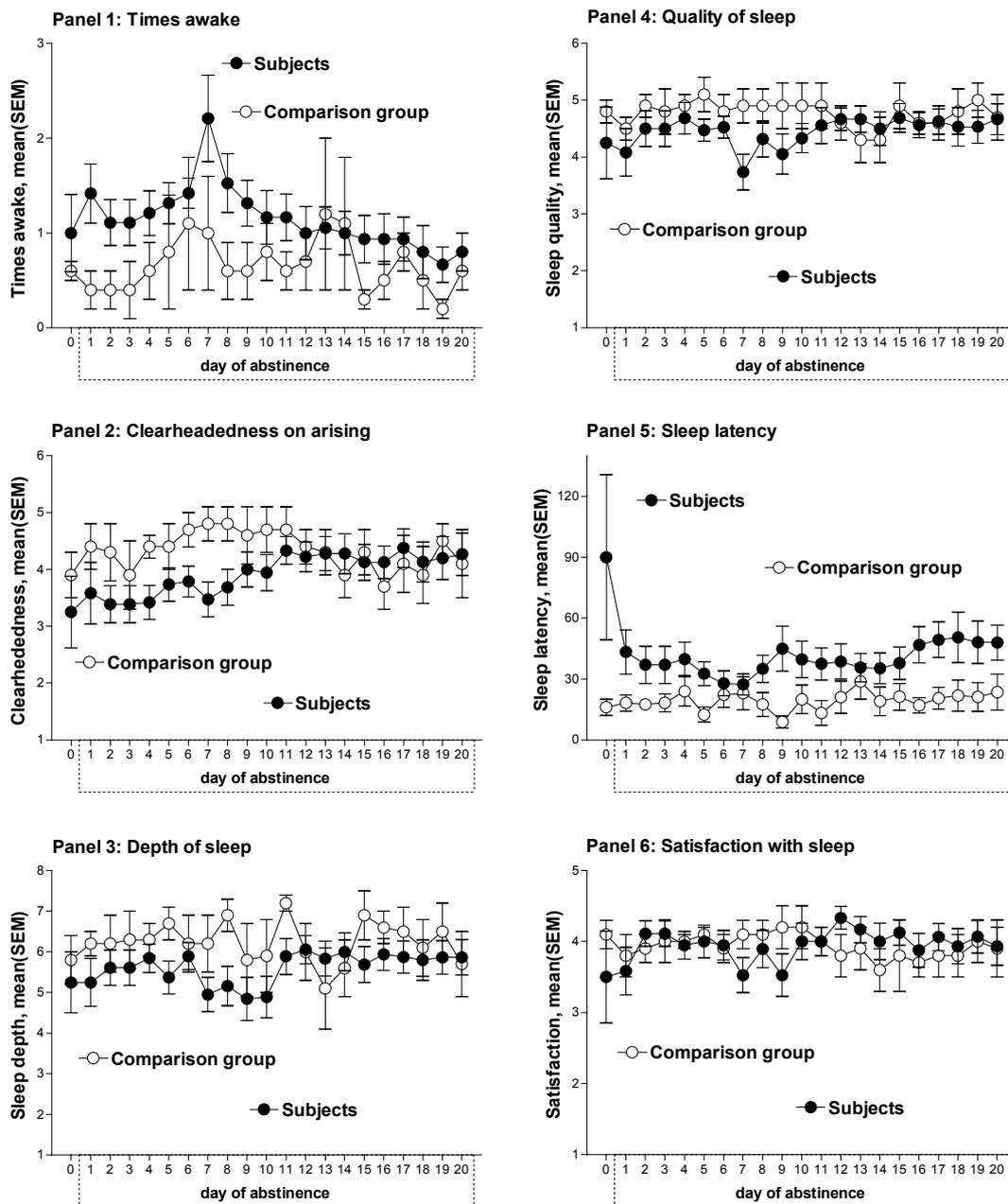
There were significant differences between groups in terms of the number of night time awakenings (F = 28.9, df 1,472 p < 0.001) (see **Figure 3.12: Panel 1**) clearheadedness on arising (F = 8.4, df 1,471 p = 0.004) (see **Figure 3.12: Panel 2**) sleep depth (F = 12.3, df 1,471 p < 0.001) (see **Figure 3.12: Panel 3**) sleep quality (F = 8.6, df 1,471 p = 0.003) (see **Figure 3.12: Panel 4**) and sleep latency (F = 49.7, df 1,470 p < 0.001) (see **Figure 3.12: Panel 5**). There were no group differences in terms of satisfaction with night time sleep (see **Figure 3.12: Panel 6**).

3.3.6.2.   *Relationship between hours of sleep prior to admission and sleep characteristics*

Inpatients were asked to estimate the total number of hours of sleep in the week prior to admission for treatment. The median number of hours of sleep in the seven days prior to admission to the inpatient clinic was 63, range 14 – 154 hours. There were weak positive relationships between the number of hours of sleep in the week prior to admission and hours of sleep per day during inpatient treatment (r = 0.12, p = 0.05), sleep depth (r = 0.27, p = 0.01) and the quality of night time sleep during the study period (r = 0.26, p = 0.01). There was a weak negative relationship between sleep prior to admission and the number of times subjects woke up during the night (r = -0.19, p = 0.01). Therefore, subjects who had slept more in the week prior to admission experienced a greater quality of sleep on some sleep characteristics during inpatient treatment.

3.3.6.3.   *Predictors of sleep patterns during withdrawal*

Using the total AWQ score as the dependent variable, linear regression analysis was performed to identify predictors of withdrawal severity during the first three weeks of abstinence. Using the standard method, three continuous variables were entered into the regression model: age, length of methamphetamine use and number of DSM-IV amphetamine dependence criteria met. Although the model was significant (F = 29, df 3,346 p < 0.001), only 21% of the variance in withdrawal scores was predicted. Multicollinearity was satisfactory: the highest correlation between independent variables was r = 0.27 between age and DSM-IV criteria. All three independent variables were significant positive predictors of withdrawal

severity: years of age (β = 0.33, *p* < 0.001), years of methamphetamine use (β = 0.27, *p* < 0.001) and number of DSM-IV amphetamine dependence criteria met (β = 0.11, *p* = 0.03).

3.3.7. Relationships between instruments used to measure withdrawal

Table 3.5 shows the relationships between summary scores of the AWQ during the first three weeks of abstinence and the interviewer-administered Amphetamine Selective Severity Assessment (ASSA), the Amphetamine Craving Questionnaire (ACQ) and the observer-rated Clinical Global Impressions (CGI) scale. All correlations were moderately strong, indicating satisfactory agreement between the scales used to measure withdrawal phenomena.

Table 3.5   ***Relationships between instruments used to measure withdrawal symptom severity***

Total	AWQ	ASSA	CGI	ACQ
AWQ		0.60	0.55	0.55
ASSA	0.60		0.64	0.37
CGI	0.55	0.64		0.41
ACQ	0.55	0.37	0.41	

All correlations significant at *p* < 0.01

3.3.8. Comparison of Australian and Thai samples

Direct comparison between the Australian and Thai samples undergoing withdrawal management was not part of the study design as there were many potential sources of bias. However, an exploration and discussion of similarities and differences between the two groups may illuminate some aspects of the amphetamine withdrawal syndrome. In addition to any cultural dissimilarity, another important group difference was the route of administration. At the time of treatment entry, all Australian subjects were currently injecting, while all Thai subjects were smoking amphetamines (inhaling the vapour from heated

amphetamine tablets). Additionally, Australian subjects had a medicated withdrawal (see **Section 2.2.11.1 above**) while Thai subjects received minimal medication (see **Section 3.2.13 above**). Finally, there was only one female subject in the Thai group, while women comprised over half of the Australian sample.

To identify differences between the two samples, data from the first eight days (days 0 – 7 of abstinence) from the Thai subjects were compared to the eight days of data (days 0 – 7 of abstinence) provided by Australian subjects. A number of marked differences were identified. Australian subjects were significantly older (mean = 29.8, SEM = 1.4 years) in comparison to Thai subjects (mean = 21.6, SEM = 0.7 years) at the time of entering treatment (t = 5.1, df 27 p < 0.001). Probably as a function of this older age, the Australian subjects had been using amphetamines significantly longer (median = 6, range 2 – 13 years) compared to Thai subjects (median = 4, range 0.75 – 15 years, U = 112, p = 0.01). There was a trend (p = 0.08) towards older age of first amphetamine use in Australian subjects (mean = 19.9, SEM = 1.17 years) compared to Thai subjects (mean = 17.2, SEM = 0.9 years).

Although Australian subjects had been using amphetamines longer, subjects in the Thai sample had used amphetamine on significantly more days in the month prior to treatment entry (all reported using every day) in comparison to Australian subjects (median = 27.5, range 12 – 30 days, U = 105, p < 0.001). Australian subjects were more dependent (as defined by scores on the SDS) on amphetamine (mean = 10.1, SEM = 0.79) in comparison to Thai subjects (mean = 6.1, SEM = 0.50, t = 4.1, df 33 p < 0.001), although there were no differences between the two samples in the number of DSM-IV criteria for amphetamine dependence that were met (p = 0.20). Australian subjects were more depressed (mean BDI score = 34.5, SEM = 3.1) on treatment entry in comparison to Thai subjects (mean BDI score = 23.6, SEM = 2.2, t = 2.9, df 38 p = 0.006).

3.3.8.1. *Comparison of symptom severity and craving in Australian and Thai amphetamine users*

Australian subjects had significantly higher AWQ scores in comparison to Thai subjects (F = 65.0, df 1,198 p < 0.001) see **Figure 3.13: Panel 1**. Similarly, ASSA scores were significantly higher in Australian subjects compared to Thai subjects (F = 117.2, df 1,198 p < 0.001) and there was a significant effect for time (F = 4.6, df 7,198 p < 0.001) see **Figure 3.13: Panel 2**.

Figure 3.13   Comparison of symptom severity and craving in Australian and Thai amphetamine users

Panel 1: Withdrawal severity (AWQ)

Panel 2: Withdrawal severity (ASSA)

Panel 3: Amphetamine craving (ACQ)
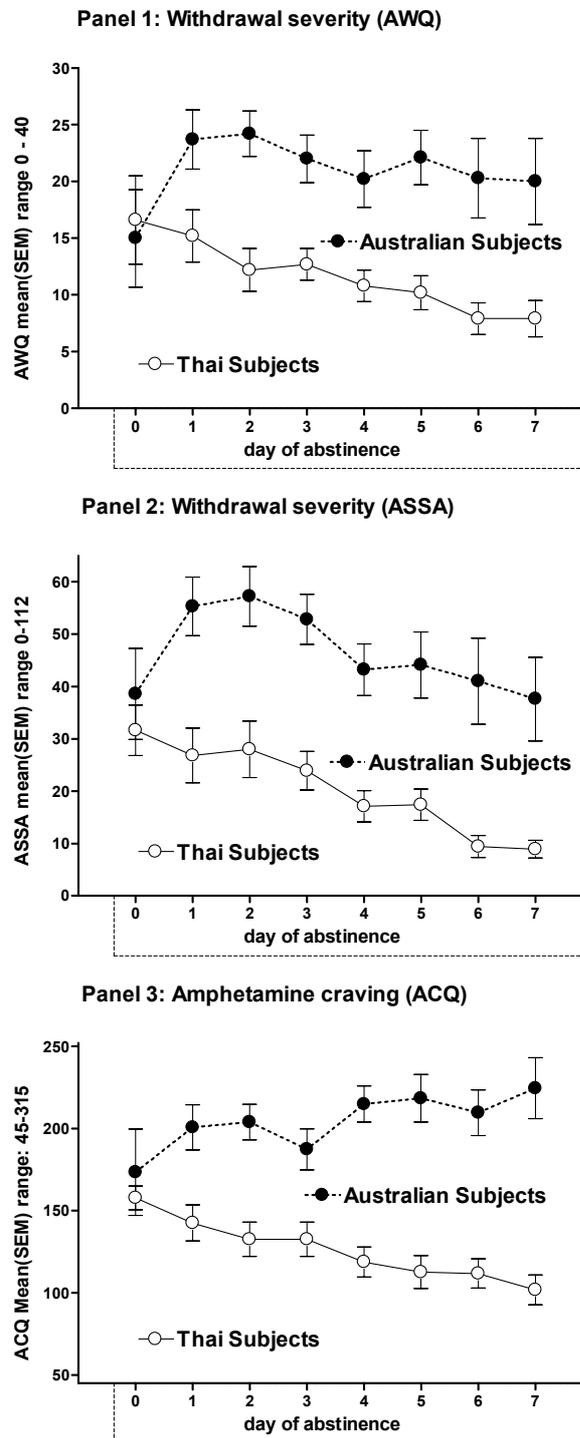
Additionally, the time course of withdrawal symptoms formed different configurations in the two groups. In Australian subjects, withdrawal symptoms increased sharply over the first 24 hours to peak on the first and second days of

abstinence while for Thai subjects, withdrawal severity peaked in the first 24 hours then declined over the first week of abstinence.

Craving scores (ACQ) were also higher in Australian subjects in comparison to Thai subjects (F = 147.1, df 1,198 p < 0.001) and there was a significant effect for time (F = 2.1, df 7,198 p = 0.006) see **Figure 3.13: Panel 3**. There were also differences in the time course of craving scores. For Australian subjects, craving increased non-significantly while for Thai subjects there was a significant decrease in craving over the first week of abstinence. There were no differences in CGI scores (data not shown).

3.3.8.2. Predictors of symptom severity and craving (combined groups)

A standard multiple regression analysis was conducted to identify significant predictors of aggregate withdrawal and craving scores and to identify the relative contribution of several independent variables and particularly, study group membership (Thai and Australian) to the variance in the total withdrawal and craving scores.

A number of models were trialled to identify the set of IVs that would best predict the aggregate withdrawal and craving scores. IVs tested in these preliminary models included study group membership (Australian or Thai), measures of amphetamine dependence, intensity of recent amphetamine use, demographic variables and amphetamine use history. The final regression model included four IVs – study group membership (Australian or Thai), severity of dependence (SDS score), years of regular amphetamine use and days of amphetamine use in the month prior to admission for treatment. Three separate regression analyses were conducted using the same IVs but using the self-reported AWQ, the interviewer-administered ASSA and the self-reported ACQ as dependent variables.

For the AWQ the model was significant (F = 47.06, df 4,209 p < 0.001), explaining 47% of the variance in withdrawal scores (adjusted R^2 = 0.46). Similarly, regression analysis for the ASSA was significant (F = 54.03, df 4,209 p < 0.001), explaining 50% of the variance in withdrawal scores (adjusted R^2 = 0.50). The model was also significant for the ACQ (F = 59.79, df 4,209 p < 0.001), explaining 53% of the variance in craving scores (adjusted R^2 = 0.52). Colinearity between

the IVs was marked, with the highest correlation being between the SDS and study group membership ($r = 0.64$). However, this level of relationship was not considered high enough to produce substantial instability in the regression analysis (Tabachnick & Fidell, 2001).

After assessing the strength of the overall regression model, an analysis of the squared semipartial correlations (Sr^2) was conducted to identify the unique contribution of each independent variable (IV) to the overall model (see **Table 3.6**). This analysis identified the SDS as the strongest predictor of self-reported withdrawal scores (AWQ), contributing around three times the variance in AWQ scores in comparison to the next two strongest predictors – length of regular amphetamine use and days of amphetamine use in previous month (all three predictors were significant).

Table 3.6   *Predictors of symptom severity and craving (combined groups)*

	AWQ		**ASSA**		**ACQ**	
			Dependent variable			
Independent variable	***Sr^2**	**p**	***Sr^2**	**p**	***Sr^2**	**p**
SDS	0.355	*0.000*	0.263	*0.000*	0.180	*0.000*
Length of regular amphetamine use	0.115	*0.022*	0.056	*0.249*	0.135	*0.004*
Days of amphetamine use in previous month	-0.111	*0.027*	-0.001	*0.982*	-0.113	*0.016*
Study group membership	0.054	*0.279*	0.223	*0.000*	0.220	*0.000*

*Squared semipartial correlation

Study membership was the weakest of the four IVs, making a non significant contribution to the variance in self-reported withdrawal scores. This result suggested that the large difference in self-reported withdrawal severity is not solely a function of cultural group, but is strongly influenced by factors such as level of dependence and the duration of amphetamine use. While the SDS was also the

strongest predictor of withdrawal scores assessed by the interviewer-administered ASSA, the contribution of study group membership to the variance in withdrawal scores was also marked. In contrast, the length of regular amphetamine use and days of amphetamine use in the previous month were relatively weak and non-significant predictors of ASSA scores. This finding reinforces the importance of the level of amphetamine dependence as mediating the intensity of withdrawal symptoms even when assessed by an interviewer. However, study membership had a greater role in interviewer assessed withdrawal severity suggesting that cultural factors may have played a part in the assessment. Interestingly, although all four independent variables (IVs) were significant predictors of self-reported craving (ACQ) scores, study group membership was the strongest predictor suggesting that cultural factors may also have had a role in subjects' responses to the assessment of craving-related cognitions.

These results indicate that the severity of amphetamine dependence is the strongest predictor of self-reported withdrawal severity while study group membership (Australian or Thai) had little predictive value. However, both the severity of dependence and study group membership influenced interviewer-administered withdrawal severity and craving for amphetamines.

3.3.8.3. Comparison of sleep characteristics and sleep patterns in Australian and Thai amphetamine users

Thai subjects reported more hours of sleep (median = 63, range 14 – 154 hours) compared to Australian subjects (median = 19, range 5 – 93 hours) in the week prior to treatment entry (U = 49, p < 0.001). However, during the first 0 – 7 days of abstinence, there were no differences between the two samples on hours of sleep during the day or night despite the use of sedation in the Australian subjects. In terms of sleep characteristics, Thai subjects were significantly more clearheaded on arising in comparison to Australian subjects (F = 14.8, df 1,191 p < 0.001). Thai subjects reported significantly greater sleep satisfaction in comparison to Australian subjects (F = 25.5, df 1,191 p < 0.001) and had significantly fewer night time awakenings (median = 1, range 0 – 7) in comparison to Australian subjects (median = 2, range 0 – 7, U = 3959, p = 0.007). There were no differences

between the two samples on sleep latency or the depth, or quality of night time sleep.

3.4. Discussion

In this study, the natural history of amphetamine withdrawal during the first three weeks of abstinence was quantified. Overall symptom severity as measured by self-report, interviewer-administered, and observer-rated instruments 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. Inspection of the data identified two phases: an acute phase that occurred during the first week, and a sub-acute phase lasting for at least two further weeks. Withdrawal severity was greater in those inpatients who were older, more dependent and who had been using amphetamine longer.

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. Less severe symptoms of amphetamine withdrawal included anxiety, motor retardation, agitation, vivid dreams, amphetamine craving, poor concentration, irritability, and tension. 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). The relative increase in bradycardia during weeks two and three possibly reflected a rebound phenomenon in cardiac function following cessation of acute withdrawal. Levels of paranoid and suicidal ideation remained low throughout the first three weeks of abstinence.

The increase in total hours of sleep between pre-admission and the peak at day five when subjects slept for around 11 hours was striking. However, there was no insomnia following the 'crash'. 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 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 inpatients had a greater total amount of sleep, in contrast to the comparison group 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. The average sleep onset latency of around 19 minutes in control subjects fell within the range for normal health adults (Ohayon, 1996) as did the total hours of sleep of around seven hours (Carskadon & Dement, 1994).

The findings from the present study also contrast with an earlier investigation into sleep duration in hospitalised amphetamine users in the United Kingdom (UK) (Gossop *et al.*, 1982). This study found 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 might be dose-related. The identification 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.

As for the previous study (see **Chapter 2**), there were no directly measurable amphetamine withdrawal signs. 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 a patient in amphetamine withdrawal.

Although almost three-quarters of the inpatient subjects in this 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 of abstinence. As for the first withdrawal study, these findings do not support previous reports showing prolonged depression following cessation of dependent amphetamine use (Watson *et al.*, 1972; Rawson *et al.*, 2002) at least in the majority of patients undergoing inpatient withdrawal treatment.

3.4.1. Comparison of Australian and Thai amphetamine users undergoing withdrawal treatment

Comparison of the present sample and the Australian amphetamine users described in **Chapter 2** identified some marked differences. However, any interpretation of these differences must take several sources of bias into account, specifically: cultural differences, environmental factors, the differing forms of amphetamine used, different route of administration, medications administered during treatment and the gender imbalance of the two samples. Additionally, the Australian amphetamine users were older and had been using amphetamines longer.

The demographic characteristics of the Thai sample were comparable to other samples of Thai amphetamine users in treatment (Srisurapanont *et al.*, 1999, 1999), while the mean age for the Australian sample was within the range identified by Baker and colleagues in their review of the characteristics of regular amphetamine users in Australia (Baker, Boggs & Lewin, 2001). Additionally, the gender balance (or imbalance) in the Thai sample is consistent with other treatment-seeking samples of substance users in Thailand where female subjects usually form a small minority of the sample (Verachai *et al.*, 2001). Conversely, it is more usual to find ratios of around 60:40 males to females in Australian samples of amphetamine users (for review see Baker *et al.*, 2001).

Differences between the two groups in the forms of amphetamine used and the route of administration make direct comparisons in terms of intensity of amphetamine use difficult. That is, Australian subjects were injecting amphetamine, predominantly in crystalline form, while Thai subjects were smoking or inhaling the vapours produced by heating methamphetamine tablets on foil. Although Thai subjects had used amphetamines on a greater number of days in

the month prior to treatment entry, Australian subjects were more dependent on amphetamines, and had greater levels of depression on treatment entry. Furthermore, although there were no differences between the two groups in observer-rated withdrawal severity, the average scores for Australian subjects on withdrawal and craving questionnaires were around twice those reported by Thai users during the first week of abstinence. Therefore, subjective but not objective withdrawal severity was markedly higher in Australian subjects despite the greater frequency of amphetamine use in Thai subjects.

A number of factors may account for the large differences in self-reported withdrawal severity. For example, it is possible that the more severe withdrawal syndrome identified in the Australian sample was associated with factors such as older age, route of administration and greater exposure to amphetamine because of their longer history of use. Greater psychological morbidity has been identified in injecting amphetamine users compared to amphetamine users who employ other routes of administration (Hall *et al.*, 1996). Cultural and environmental factors may also mediate the experience and reporting of withdrawal symptoms. For example, there is less acceptance of 'complaining' in Thai culture and the author noted that patients appeared to minimise or deny discomfort at times. Additionally, the Thai clinic environment, where a large number of young men were grouped together may have mediated the experience of inpatient withdrawal treatment. That is, while there were some episodes of friction, patients largely supported and encouraged each other during treatment and there was a strong sense of camaraderie among the patient population.

However, when differences between Australian and Thai subjects were further explored using regression techniques, the severity of dependence was identified 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 self-reported withdrawal. In contrast, study membership was the weakest of the four IVs, contributing little to the patients' perception of withdrawal severity. This result 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.

However, study group membership made a greater contribution to the variance in ASSA scores, although the SDS was still the strongest predictor. In contrast to self-reported withdrawal, the length of regular amphetamine use and days of amphetamine use in the previous month were relatively weak and non-significant predictors of ASSA scores. This finding reinforced the importance of the level of amphetamine dependence as mediating the intensity of withdrawal symptoms even when assessed by an interviewer. However, study membership had a greater role in interviewer-assessed withdrawal severity suggesting that cultural factors may have played a part in the interviewer-administered assessment.

Conversely, although the severity of amphetamine dependence and the duration and intensity of amphetamine use were significant predictors of self-reported craving scores, study group membership was the strongest predictor suggesting that cultural factors may also have had a role in subjects' responses to this instrument.

These results indicate that the severity of amphetamine dependence followed by the duration and intensity of amphetamine use are the strongest predictors of self-reported withdrawal severity while study group membership (Australian or Thai) had little predictive value. However, both the severity of dependence and study group membership mediated interviewer-administered withdrawal severity and self-reported craving for amphetamines.

Although Thai subjects had slept more during the week prior to treatment entry there were no differences in hours of sleep during the first week of withdrawal despite the use of sedation in the Australian subjects. Interestingly, Thai subjects were more clearheaded on arising and had greater sleep satisfaction with fewer night time awakenings.

3.4.2. Limitations of the study

There are several limitations of this study. The comparison group participants, who were seen daily at their place of work or study, were not tested under exactly the

same conditions as inpatients. 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.

3.4.3. Summary

This study has provided the first published data on the natural history of amphetamine withdrawal in human subjects (McGregor, Srisurapanont, Jittiwutikarn, Laobhripatr, Wonttan & White, 2005). Several validated instruments measuring diverse withdrawal phenomena were administered on multiple occasions over the first three weeks of abstinence and the resulting data compared to that from normal, healthy individuals. Inspection of the data showed that the amphetamine withdrawal syndrome identified in this study could be categorised into two phases: an acute phase lasting 7 – 10 days following cessation of dependent use during which overall symptom severity declined in a linear pattern from a high initial peak. This was followed by a sub-acute phase lasting at least two weeks following the end of the acute phase during which most withdrawal symptoms remained relatively mild and stable. During the acute phase, inpatients undergoing amphetamine withdrawal had increased sleeping and eating, depression-related symptoms and, less severely, anxiety and craving-related symptoms. Withdrawal severity was greater in those inpatients who were older, more dependent and who had been using amphetamine longer. Oversleeping was marked during the acute phase and despite a reduction in quality, was not followed by a period of insomnia during the sub-acute phase.

See **Appendix 3** for the publication that arose from the work described in this chapter (McGregor *et al.*, 2005).