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**THE TIME-DEPENDENT EFFECTS OF BENZODIAZEPINES ON IMPLICIT AND
EXPLICIT MEMORY**

By

Susan Elizabeth Buffett-Jerrott

**Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy**

at

**Dalhousie University
Halifax, Nova Scotia
September, 2000**

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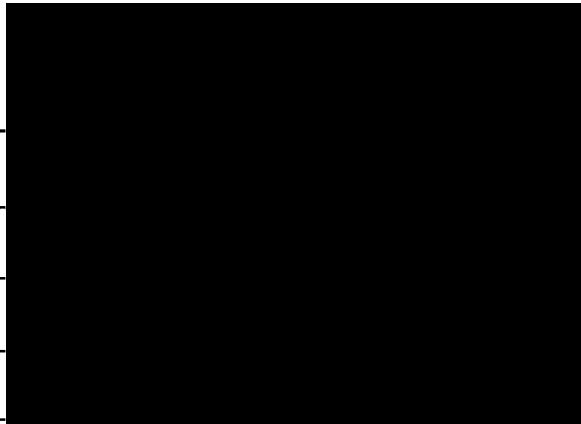
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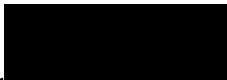
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Dedication

This work is dedicated to my beautiful daughter, Emma Kathleen Elizabeth Jerrott. Looking into her incredible blue eyes and seeing her smile was an intense motivator to finish this manuscript and devote more time to mothering.

The soul is healed by being with children.

Fyodor Dostoyevski

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Abstract

Three studies examined the time-dependent effects of benzodiazepines (BZs) on implicit and explicit memory. Study 1 investigated the hypothesis that BZs would impair implicit memory if participants encoded the to-be-remembered stimuli around the time of the peak blood concentration of the drug. The effects of 2 mg lorazepam, 30 mg oxazepam, and placebo were examined by comparing the effects of each drug on implicit and explicit memory at 170 minutes post-drug. This time point is close to the peak blood concentration time for oxazepam and past the peak concentration time for lorazepam. Results indicated that both BZs impaired explicit and implicit task performance. Study 2 was designed to examine the time-dependent memory impairment curve of a single BZ, oxazepam. The effects of 30 mg oxazepam and placebo on implicit and explicit memory tasks were studied at 100 minutes (pre-peak), 170 minutes (peak) and 240 minutes (post-peak) after drug administration in a between-subjects design. Results indicated that at “pre-peak”, only explicit memory was impaired by oxazepam. However, in the “peak” condition, oxazepam impaired performance on both memory tasks. In the “post-peak” condition, explicit memory was impaired, but priming impairments were beginning to wane. Study 3 was designed to replicate and extend the findings of Studies 1 and 2 to an applied setting. Study 3 used a placebo-controlled design to examine the effects of 0.50 mg/kg oral midazolam at two encoding times (pre-peak and peak) in children who were undergoing myringotomy surgery. The results indicated that explicit memory was impaired by midazolam at both encoding times. However, in contrast to findings with pilot participants, the priming task did not adequately assess implicit memory in the hospital situation. Results are discussed in terms of their implications for theories of memory organization and their clinical applications.

List of Abbreviations

AD	antidepressant
AzD	Alzheimer's Disease
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APA	American Psychological Association
BMA	bone marrow aspiration
BMDP	Bio-Medical Data Program
BMI	body mass index
BZ	benzodiazepine
CBT	cognitive behavioural therapy
CFFT	Critical Flicker Fusion Threshold
CNS	central nervous system
DAST	Drug Abuse Screening Test
DRTT	Discriminant Reaction Time Task
DSST	Digit Symbol Substitution Test
FTT	Finger Tapping Test
GABA	gama-aminobutyric acid
GAD	Generalized Anxiety Disorder
G.I.	gastrointestinal
i.m.	intramuscular
i.v.	intravenous

LCT	Letter Cancellation Task
LP	Lumbar Puncture
MAST	Michigan Alcoholism Screening Test
MDT	Motor Deletion Task
mYPAS	Modified Yale Preoperative Anxiety Scale
NA	noradrenaline
N₂O	Nitrous Oxide
PD	Panic Disorder
PDP	Process Dissociation Procedure
PDTP	Picture Deletion Test for Preschoolers
PHBQ	Post Hospitalization Behaviour Questionnaire
p.r.n.	as needed
PRS	Perceptual Representation System
RT	reaction time
SCT	Symbol Copying Test
SIL	ShIPLEY Institute of Living Scale
SOA	stimulus onset asynchrony
SYCT	Symbol Cancellation Task
™	trademark
VAS	Visual Analogue Scale
WMS-R	Wechsler Memory Scale-Revised
5-HT	serotonin

Publication Citation

Portions of the research presented in this thesis have appeared in published form and/or presented at conferences:

A modified version of the introductory chapters has been accepted for publication in *Current Pharmaceutical Design* (in press).

Study 1 has been published in abridged form in *Psychopharmacology*, 1998, Vol. 138, 344-353. Abstracts from this work can be found in the *Program and Abstracts of the 7th Annual Meeting of the Canadian Society for Brain, Behavior, and Cognitive Science*, 31 and 46.

Study 2 has been published in abridged form in the *Journal of Psychopharmacology*, 1998, Vol. 12, 369-378. An abstract from this work can be found in *Canadian Psychology*, Vol. 36 (2a), 55.

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There are many other unnamed persons who encouraged me to strive to reach my academic and clinical goals over the years. I am grateful to all of them.

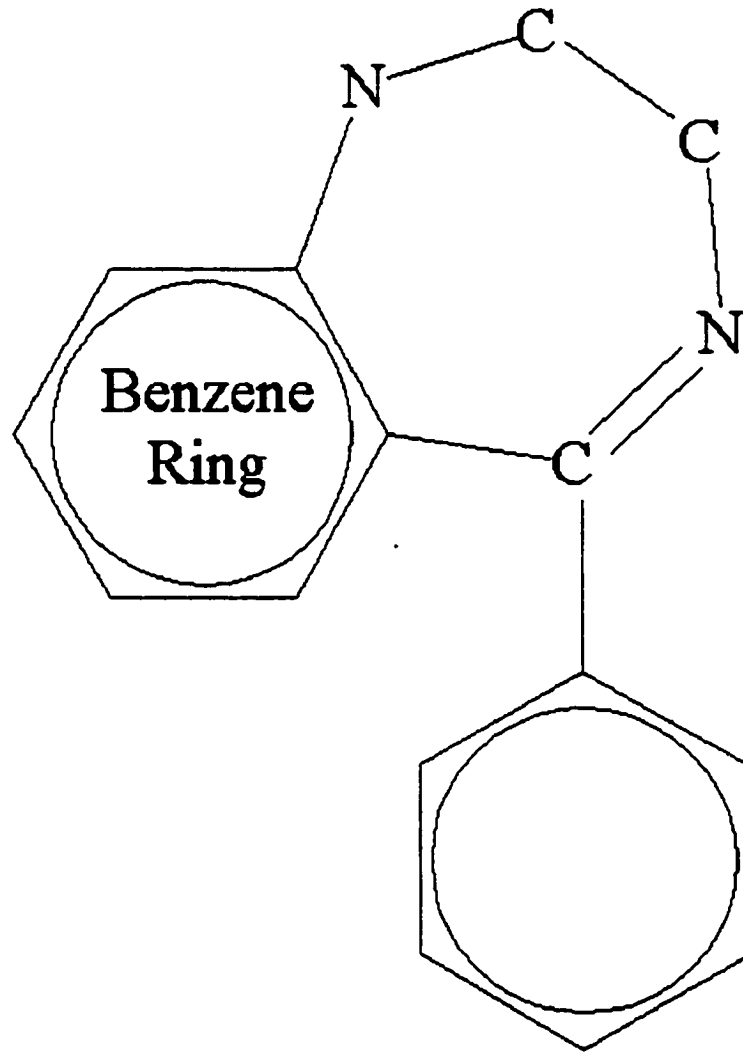
CHAPTER ONE:

Benzodiazepines: Epidemiology, Mode of Action and Clinical Factors

Benzodiazepines (BZs) are a class of drugs with anxiolytic, sedative, hypnotic, and muscle-relaxant properties. In clinical practice, BZs are commonly used in the treatment of anxiety and insomnia. Until the late 1960's symptoms of anxiety and insomnia were usually treated with barbiturates (Hamlin, 1993). However, these drugs tended to cause dependence and severe withdrawal reactions, and had limited efficacy in treating anxiety (Sloan & Wala, 1998). In addition, they had a dangerous potential for coma and death if an overdose occurred (Sloan & Wala, 1998). When BZs were developed, it became apparent that they were more effective in treating anxiety, had fewer side effects, produced less dependence, and were safer than barbiturates (Moller, 1999). For these reasons, BZs quickly replaced barbiturates as the primary pharmacological treatment of anxiety (Hamlin, 1993). In addition to the treatment of anxiety symptoms, BZs are also prescribed for their muscle relaxant, sedative-hypnotic and anticonvulsive effects (Health and Welfare Canada, 1982).

The basic structure of a benzodiazepine includes a benzene ring fused to a 7-membered ring that has nitrogen atoms in the 1 and the 4 positions (see Figure 1) (Sloan & Wala, 1998). This structure is somewhat similar to that of the barbiturates, which consist of a 6-membered ring with attached nitrogen atoms (Sloan and Wala, 1998), but quite different from alcohol, which consists of a hydrocarbon chain with a hydroxy group attached to one carbon (Hunt, 1998).

Figure 1: Basic Chemical Structure of a Benzodiazepine: Author's depiction adapted from Sloan and Wala (1998).



The first BZ, chlordiazepoxide (Librium™), was introduced in Canada in 1960, followed two years later by the introduction of diazepam (Valium™) (Health and Welfare Canada, 1982). Diazepam quickly became the most commonly prescribed psychotropic drug in North America. Since 1960, over 50 different BZs have been introduced into clinical practice (Medina, Paladini, & Izquierdo, 1993), with alprazolam (Xanax™) currently being the most commonly prescribed (Gold, Miller, Stennie, & Populla-Vardi, 1995; Health Central, 1999). In 1980, over 1 billion doses of a BZ per day were taken worldwide (Hamlin, 1993). In the last 20 years, the use of BZs has declined significantly (Woods & Winger, 1995). This decline is likely due to increased awareness that BZs were being over-prescribed, and of their risk of dependence, withdrawal, and cognitive side effects (Shader, Greenblatt, & Balter, 1991). In addition, drugs were introduced that were as effective as BZs in treating anxiety but that had fewer side-effects and less potential for withdrawal and dependence (e.g., buspirone – a serotonin partial agonist) (Laakmann et al., 1998). Despite this decline, BZs still remain the most widely prescribed anxiolytic agent in the world today (Longo, 1998a) with 10% of the adult population ingesting at least one BZ in a one-year period for a reason other than insomnia (Gold et al., 1995). The typical user of BZs is elderly and female (Michelini, Cassano, Frare, & Perugi, 1996). The fact that females are more likely to be BZ users may reflect both the greater prevalence of anxiety disorders in females than males (DSM-IV; APA, 1994) and/or physician prescription biases involving over-prescriptions to women (Hohmann, 1989).

A great deal of research has been conducted to determine the specific anxiety disorders that can be effectively treated with BZs. A meta-analysis conducted on the treatment of generalized anxiety disorder (GAD) (Gould, Otto, Polack, & Yap, 1997)

found that BZs were an effective treatment for GAD. When BZs were compared to other pharmacological treatments (e.g. buspirone) and cognitive behavioral therapy (CBT) in the treatment of GAD, the meta-analysis indicated no difference between the efficacies of the treatments in the short-term. However, both pharmacological groups appeared to show some “slippage” of treatment gains over time, while the treatment gains associated with CBT were maintained. In a study that directly compared buspirone (a partial agonist at the serotonin-1A receptor) and lorazepam (a BZ) in the treatment of GAD, both drugs were found to be equally effective (Laakmann et al., 1998). However, buspirone had a gradual onset of clinical effects, while the effects of lorazepam were almost immediate. Alternatively, when the drugs were tapered, the lorazepam group showed significant withdrawal effects, as compared to the buspirone group.

In a similar meta-analysis on the treatment of panic disorder (PD) (Gould, Otto, & Pollack, 1995), results indicated that BZs are an effective treatment for PD. This analysis indicated that antidepressant (AD) therapy was also effective in the treatment of PD, and that there was no difference in BZ and AD effectiveness. It should be noted, however, that cognitive-behavioral therapy (CBT) was found to be at least as effective, or more effective, than BZs in the treatment of PD. In the treatment of social phobia, BZs have also been found to be an effective treatment (Sutherland & Davidson, 1995).

Research also indicates that BZs are an established short-term treatment for insomnia. However, BZs are not effective in the long-term treatment of insomnia due to the eventual development of tolerance to the sedative effects of the drug (Longo & Johnson, 1998).

BZs also have established use in the hospital as preoperative medicants, and for emergency sedation (Moller, 1999). There is also good evidence supporting the effectiveness of BZs for the treatment of psychotic agitation, involuntary movement disorders, and cocaine/LSD intoxication (Moller, 1999). Due to their anticonvulsant effects, BZs are also commonly used during the detoxification phase in the treatment of alcoholism, in order to prevent life-threatening seizures in severely dependent alcoholics (Miller, Frances, & Holmes, 1989).

Hypothesized Mode of Action of BZs

There are three main neurotransmitters that have been hypothesized to have a direct involvement with the anxiolytic activities of the BZs (Kataoka, Shibata, Yamashita, & Ueki, 1987). These neurotransmitters are GABA, noradrenaline, and serotonin.

GABA. Gamma-aminobutyric acid (GABA) is a neurotransmitter that is much more widely distributed than serotonin and noradrenaline, and is present in as many as one-third of all synapses in the human brain (Haefely, 1993). GABA is the major inhibitory neurotransmitter in the brain, and increases in GABA appear to be associated with a reduction in anxiety (Leonard, 1993). Alcohol and barbiturates have been found to produce their sedative and anxiolytic effects by facilitating the transmission of GABA in neural centers associated with anxiety production (Longo, 1998).

The BZ Receptor Complex. Early research indicated that the BZs do not act directly on the GABA receptors, as the barbiturates do, but instead seem to indirectly affect inhibitory neural transmission via GABA (Polc & Haefely, 1977). There are two main types of GABA receptors in the brain: GABA_A and GABA_B receptors (Haefely, 1990). It appears that GABA_B receptors are associated with potassium ions, and that they do not interact

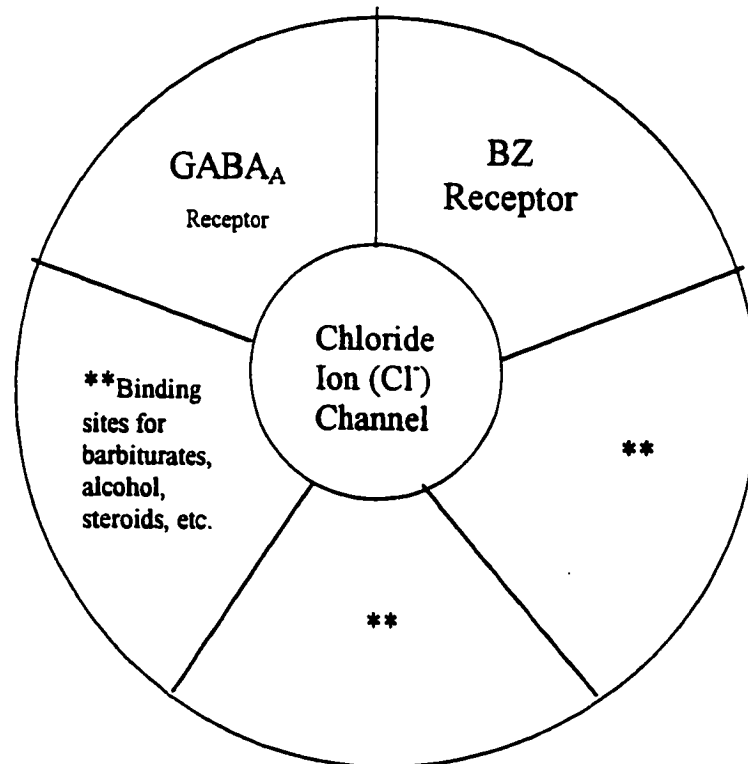
with BZs (Haefely, 1990). GABA_A receptors are associated with sites that have been termed BZ receptors because the BZs have a high affinity for these sites. GABA_A receptors are also associated with sites for alcohol, barbiturates and steroids (Belelli, Lan, & Gee, 1990). Overall, BZ receptors are most prevalent in the neocortical regions of the brain, with intermediate levels in the cerebellum and limbic structures (structures implicated in anxiety production; Gray, 1995), and relatively low levels in the pons, spinal cord and medulla oblongata (Squires et al., 1979). It has been suggested that the term BZ receptor be changed to omega receptor, as compounds other than BZs also act at the receptors (Langer & Arbilla, 1988). However, this terminology has not been readily accepted in the research literature, and I will continue to use the term “BZ receptors” throughout this thesis.

There are two subtypes of BZ receptors specifically associated with the GABA_A receptor (Squires et al., 1979). These have been termed BZ₁ and BZ₂ receptors (Griebel, 1999). BZ₁ receptors are more prevalent in the cerebellum (Sanger et al., 1994), whereas BZ₂ receptors are more prevalent in the spinal cord, striatum and adrenal medulla (Kunovac & Stahl, 1995). It has been suggested that these two subtypes of BZ receptors might be responsible for different effects of BZs (Griebel et al., 1999). Recent research indicates that BZ₁ sites may be responsible for the anxiolytic and sedative/hypnotic effects of BZs, and that the muscle relaxant effects may occur at the BZ₂ site (Griebel et al., 1999). In addition, some research suggests that only BZ₂ receptors are associated with the amnesic effects of BZs (Sanger et al., 1994).

BZ receptors and GABA receptors tend to be coupled in protein complexes on neurons throughout the central nervous system. These complexes have been termed

GABA supra-molecular receptor complexes (see Figure 2) (Roy-Byrne & Nutt, 1991). These complexes have five subunits in addition to a chloride ion channel. In the absence of GABA, BZs do not have any effect on the chloride channel (Medina et al., 1993). However, when a BZ binds to the BZ receptor, it changes the structure of the GABA receptor, so that GABA's binding to the GABA receptor is enhanced, and the frequency of the chloride channel opening is increased, allowing chloride ions to diffuse into the neuron (Longo, 1998b). This influx of chloride increases the negative charge of the cell and makes it less likely that action potentials will occur (i.e., an "inhibitory" effect) (Haefely, 1990). The effect of BZs on the chloride channel is different than the effect of barbiturates. Barbiturates directly stimulate the chloride channel, increasing the length of time that the channel is opened, as opposed to the frequency of ion channel opening (Sloan & Wala, 1998). Some have suggested that this difference may explain why BZs are less toxic and have fewer side effects than barbiturates (Longo, 1998a). Overall, it appears that GABA has a stronger inhibitory action on the post-synaptic neuron in the presence of BZs than would occur in the absence of BZs (Leonard, 1993). Additionally, the presence of GABA increases the binding of BZs to the BZ receptors (Leonard, 1990). This has been termed the "GABA shift" (Roy-Byrne & Nutt, 1991). This interaction between two binding sites (GABA and BZ) on the same protein complex is termed "allosteric" (Haefely, 1990).

Figure 2: Schematic Model of the GABA_A Supra-Molecular Receptor Complex: Author's diagrammatic depiction based on information and figures contained in Roy-Byrne and Cowley (1991) and Haefely (1990).



Noradrenaline. This neurotransmitter is strongly related to the human stress response, and the fear-induced increase in noradrenaline (NA) appears to be reduced by the BZs. Animal studies indicate that rats can be easily trained to press a lever to receive food. However, if they also receive a shock when they press the lever, the number of lever presses is greatly reduced. Research indicates that rats that have received a BZ are more likely than non-drugged rats to press the lever in the presence of shock. It appears that the inhibiting effect of shock on behaviour is reduced by administration of BZs. In addition, it appears that it is BZ's effects on NA which produce this anti-conflict action, and that this action is not entirely facilitated by the GABA or serotonergic systems (Kataoka et al., 1987). However, recent research indicates that the effects of BZs on NA may be temporary, and may actually be related to the sedative effects of the BZs, as opposed to their anxiolytic effects (Leonard, 1993).

Serotonin. Research indicates that a reduction in serotonin (5-HT) may have an anxiolytic effect, and that BZs tend to reduce 5-HT levels in the central nervous system (CNS) (Collinge, Pycock & Taberner, 1983). The hypothesis that 5-HT is affected by the BZs is indirectly supported by the development of new anxiolytics (e.g., buspirone) that act directly on the serotonergic receptors and decrease the function of 5-HT (Sloan & Wala, 1998). However, recent studies suggest that most of the reduction in 5-HT levels by the BZs is actually an indirect effect of BZ influences on GABA, since GABA acts via a presynaptic mechanism at the serotonergic nerve terminal to regulate the release of 5-HT (Lista, Blier, & DeMontigny, 1990a). In fact, BZs' effects on 5-HT are blocked by the administration of the GABA_A-specific antagonist bicuculline (Lista, Blier, & DeMontigny,

1990b). However, the specific mechanism of the effects of GABA on 5-HT is not yet fully understood (Collinge et al., 1983).

Summary. Presently, most research indicates that the major action of the BZs is to facilitate the transmission of GABA – an inhibitory neurotransmitter thought to play a role in anxiety regulation. This facilitation has effects on other neurotransmitter systems, leading to changes in the brain levels of NA and/or 5-HT. These secondary changes, however, may also play a role in the anxiolytic therapeutic action of the BZs (see review by Leonard, 1993).

The Search for Natural (Endogenous) BZs. Since receptors for BZs exist in the brain, it is logical to assume that a compound similar to the BZs is ingested in our food or created in our bodies. Many different molecules have been hypothesized to be endogenous ligands for the BZ receptors, but no conclusive evidence has been acquired (Bradwejn & De Montigny, 1985). These molecules have been found to bind to the BZ receptors and act as agonists or antagonists. Agonists (e.g. BZs) are substances that bind to most GABA_A receptors and facilitate GABA_A receptor function (Miller, Klamen, & Costa, 1998). Inverse agonists (e.g., beta-carboline) are substances that inhibit the effects of GABA_A receptor function (Nutt, 1990). Antagonists (e.g. flumazenil) are substances that block the effects of both agonists and inverse agonists at the receptor (Nutt, 1990). Interestingly, some of these substances, such as PK 8165, act as partial agonists (substances that bind to the GABA_A receptors but produce only some of the effects of full agonists). PK 8165 has an anxiolytic quality at low doses but at high doses blocks the effects of BZs (Bradwejn & De Montigny, 1985). Recently, researchers found small levels of BZs in the milk of lactating women who were not users of BZs (Medina et al., 1990). Studies indicate that

an average baby who suckles 250 ml of milk in a day is ingesting the equivalent to 500 ng of diazepam per day (Medina et al., 1993). BZs have also been found in the brains of non-medicated individuals. The highest concentrations of these molecules were found in the medial septum, amygdala, and hippocampus (Wolfmann et al., 1991). It is not yet known if these natural BZs are ingested in our food, formed in the brain, or biosynthesized by microorganisms in the gastrointestinal tract (Medina et al., 1993).

Pharmacokinetics and Pharmacodynamics of the BZs

Pharmacokinetics. The term pharmacokinetics describes the process in which drugs are absorbed in the gastrointestinal (G.I.) tract, distributed to various tissues within the body, metabolized, and eliminated from the body (Cowley, Roy Byrne & Greenblatt, 1991).

Before reaching the brain, oral doses of BZs have to be absorbed by the G.I. tract.

Overall, oral BZs tend to be absorbed rapidly from the G.I. tract and the proportion of an oral dose that is absorbed from the G.I. tract and reaches systemic circulation is very high (Cowley et al., 1991). The absorption of oral BZs can be slowed by the presence of food in the stomach (Feely & Pullar, 1990). However, food in the stomach does not alter the total amount of drug absorbed (Cowley et al., 1991). In contrast to orally administered BZs, intravenous (i.v.) BZs are not absorbed in the G.I. tract and are not affected by factors such as the amount of food in the stomach. The distribution rate of a BZ depends on the time it takes the drug to reach the brain, cross the blood-brain barrier by passive diffusion, and reach the receptor sites (Cowley et al., 1991). Therefore, less lipophilic BZs (e.g. lorazepam) have a very slow onset of action compared to other, strongly lipophilic BZs (e.g. diazepam) because they are slower to enter the central nervous system (Greenblatt et al., 1989). BZs have been subdivided into fast acting (e.g., midazolam),

intermediate acting (e.g., lorazepam) and slow acting (e.g. oxazepam) subgroups on this basis (American Psychological Association [APA] Task Force, 1990). Overall, the speed of onset of BZ effects is mainly dependent on how quickly the drug reaches the BZ receptors (Cowley et al., 1991).

Some of the benzodiazepines (e.g. diazepam) go through several metabolic transformations (forming active metabolites), before they are cleared from the body (APA Task Force, 1990). However, other BZs (e.g., lorazepam, oxazepam and midazolam) do not go through these transformations, and do not produce active metabolites. BZs that go through multiple metabolic steps take more time to be cleared from the body, overall (APA Task Force, 1990). The term “elimination half-life” refers to the time it takes the concentration of a drug in the body to fall by 50%. BZs are classified as having ultra-short (e.g., midazolam, triazolam), short-intermediate (e.g., oxazepam, lorazepam) or long half-lives (e.g., diazepam) (Greenblatt, Shader, Divoll, & Harmatz, 1981). Half-life is very important when prescribing BZs for chronic administration. When given regularly, the blood level of the BZs will reach steady state in about five half-lives (APA Task Force, 1990). Therefore, it takes quite a long time to reach steady state with drugs that have long half-lives. However, there are also problems with using drugs with short half-lives, as many patients have breakthrough symptoms between doses, and withdrawal effects (e.g., insomnia, anxiety, tension, restlessness, agitation) can occur if a patient misses even one dose of their BZ (Duncan, 1988).

Pharmacodynamics. The term pharmacodynamics describes the intensity and time course of the interaction between a drug and its receptors. The pharmacodynamics of the BZs concern their interactions with the GABA receptor sites (Cowley, Roy-Byrne, &

Greenblatt, 1991). Different BZs require different doses to produce the same clinical effects (i.e., 15 mg of oxazepam are needed to produce the same anxiolytic, attentional and sedative effects induced by 1 mg of lorazepam [Curran & Gorenstein, 1993; Curran, Schiwy, & Lader, 1987]). This is because the drugs differ in the characteristics of their receptor binding, and the extent of their entry into the CNS. Some drugs have more affinity for the benzodiazepine receptors than others and, therefore, are termed more “potent”. The duration of action of specific BZs is dependent on how extensively they are distributed. In fact, drugs with long half-lives may still have a short duration of action if they undergo very rapid or extensive distribution throughout the brain (Greenblatt, 1995). BZs such as lorazepam and midazolam bind very rapidly with BZ receptors and are, therefore, considered more potent than BZs such as oxazepam and diazepam (Tyrer, 1993).

Clinical Factors Associated with Administration of BZs

Although the number of BZ prescriptions has declined world-wide, it is estimated that one in four users of BZs has been taking these drugs continuously for one year or longer (Woods & Winger, 1995) with most BZ prescriptions coming from general practitioners and internists (Michelini et al., 1996). As noted by Nutt (1990), BZs are likely to be the most controversial group of psychotropic drugs currently in use. Although 75% of BZ users are content with their medication (Barnas et al., 1991), the FDA has cautioned against the long-term use of BZs because there are many clinical problems associated with their chronic administration (Greenblatt, Shader & Abernaethy, 1983). These include issues of tolerance, withdrawal, dependence, abuse, and side-effects.

Tolerance. Tolerance occurs when the effects of a drug are markedly diminished with continued use of the same amount of the drug, or when increasing amounts of a drug are needed over time to achieve the same effects as when the drug was initially prescribed (DSM-IV; APA, 1994; Potokar, Coupland, Wilson, Rich and Nutt, 1999). Tolerance is not only an index of the long-term efficacy of a drug, but is also an indication of the drug's safety profile as tolerance is often associated with the development of physical dependence (usually in conjunction with withdrawal symptoms) (DSM-IV; APA, 1994; Treit, 1985). Overall, most research indicates that many BZ effects are subject to tolerance (Nutt, 1990). There is evidence to indicate that BZ tolerance may be partially explained by changes in the function of the BZ receptors following long-term use of BZs (Leonard, 1993). It has been suggested that long-term use of BZs causes the BZ receptor to shift in the inverse agonist direction, and increasing amounts of a BZ are needed to counteract this shift (Little, Nutt, & Taylor, 1987).

There is quite a bit of controversy in the research literature regarding the idea of tolerance to the anxiolytic effects of BZs (File, Baldwin, & Aranko, 1987). In the animal literature, the majority of research indicates that tolerance is quickly developed to the anxiolytic effects of BZs. Fernandes and File (1999) found that rats initially given diazepam showed increased social interaction, thought to be a sign of decreased anxiety. However, this effect was not apparent after 21 days of BZ treatment. Likewise, File et al. (1987) and Chopin, Assie, and Briley (1993) both found that rats became tolerant to the anxiolytic effects of BZs (chlordiazepoxide and diazepam) after 20 days of treatment, as measured by an elevated plus-maze procedure. In an interesting study conducted by Treit (1985), rats did not become tolerant to the anxiolytic effects of diazepam when the

aversive stimulus was mild (low-level shock). However, when the aversive stimulus was more severe (higher-level shock), tolerance to the anxiolytic effects of the drug could be observed within 10 days of BZ treatment. These findings suggest that BZs may lose their anxiolytic action with chronic BZ administration only when the anxiety-producing stimuli are relatively severe.

Studies in the human literature are not as consistent in their findings regarding tolerance to the anxiolytic effects of BZs. In a lab-based experimental study that compared the effects of various BZs in chronic BZ users with an anxious control group, tolerance was not shown to their anxiolytic effects, as measured by equivalent subjective reporting of feelings of tranquilization on a VAS across the chronic BZ users vs. anxious control groups (Lucki, Rickels, & Geller, 1986). Likewise, a study using the State version of the State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lucshene, 1969) found that long-term BZ users rated themselves as less anxious after taking a BZ (Curran, 1992). However, this study was not placebo controlled and only chronic BZs users were examined. It is possible that the anxiolytic effects in chronic users are reduced, even if they are still present. If the anxiolytic effects are less marked than they were originally, tolerance would be suggested. A longitudinal design or a BZ-naïve control group is needed to help make this determination. Lending support to the idea that individuals do not become tolerant to the anxiolytic effect of BZs is the fact that most chronic BZ users do not increase their initial dose of a BZ (APA Task Force, 1990). However, one study actually found an increase in anxiety symptoms during the course of long-term BZ use. In fact 20% of the participants had become agoraphobic over the course of treatment, a condition that was not the original reason for the BZ medication (Ashton, 1987). In a

double-blind study, anxious outpatients were randomly assigned to receive diazepam or placebo (both combined with psychotherapy) (Shapiro, Struening, Shapiro, & Milcarek, 1983). The results indicated that within one week, diazepam significantly reduced anxiety, compared to the placebo group, as rated by the participants and their psychiatrists.

However these differences were not apparent at the next five weekly appointments. These initial results suggest that tolerance may quickly develop to the anxiolytic effects of BZs.

However, further analysis of the data indicated that highly anxious patients did show significantly increased psychiatrist-rated improvement on diazepam, as compared to placebo after a month of treatment. However, this difference was not significant at the six-week follow-up appointment, as the placebo-treated participants had also improved by this time. In contrast to the highly anxious patients, patients with moderate and low levels of anxiety did not appear to benefit from diazepam after the first week of treatment.

Overall, animal research and objective symptom checks in humans indicate that tolerance does develop to the anxiolytic effects of BZs, while most subjective ratings indicate that the anxiolytic effect remains. The fact that participants do not rate themselves as anxious may be a result of a placebo effect, in that individuals expect to feel less anxious when taking BZs. However, placebo-controlled research with long-term BZ users is needed to test this hypothesis. As noted by Curran (1992) it is also possible that chronic BZ users are experiencing withdrawal effects between doses. Initially, BZs probably have anxiolytic effects in anxious patients. However, with repeated dose administration, both withdrawal and tolerance develop, leading to dependence on the drug. Even if a patient actually becomes tolerant to the anxiolytic effects of BZs, this tolerance may be masked by BZ dampening of withdrawal symptoms that may occur

between doses. BZ dampening of withdrawal symptoms may be misinterpreted by anxious patients as “anxiolytic” drug effects. In addition, the variable results of studies on the development of tolerance to the anxiolytic effects of BZs may simply be a reflection of the different results that are obtained when using subjective versus objective measures of emotion. Lending support to this idea, one study found that participants reported decreased feelings of hostility, compared to placebo-treated participants, after eight weeks of BZ treatment. However, the same BZ-treated participants actually behaved in a more aggressive manner in response to provocation, indicating that BZs were not reducing hostility, as was believed by the participants (Bond, Curran, Bruce, O’Sullivan, & Shine, 1995). Finally, it is possible that tolerance to the anxiolytic effects of BZs is only apparent at times of severe anxiety, as suggested by the findings of Treit (1985). Obviously, more research is needed in this area. Particularly, researchers should compare objective versus subjective anxiety measures in the same study.

Although many questions remain regarding the possible development of tolerance to the anxiolytic effects of BZs, the majority of studies indicate that tolerance does develop to the some of the other effects (e.g., sedation) of BZs with chronic use (Curran, 1992). I will review research suggesting that tolerance develops differentially to the various cognitive effects associated with BZ administration in Chapter 2.

BZ Discontinuation. Although many longer-term, BZ-using patients will attempt to discontinue BZ treatment, over 50% of these individuals will be unsuccessful (Lader, 1995). Most researchers agree that BZ withdrawal does occur. However, there is considerable controversy regarding the severity and type of symptoms experienced (Michellini et al., 1996). Generally, there are three types of symptoms that can occur when

BZ treatment is discontinued (Noyes, Garvey, Cook, & Perry, 1988). *Relapse symptoms* are a return of the original symptoms (e.g., anxiety, insomnia). Relapse symptoms tend to occur gradually following discontinuation and do not disappear over time. These symptoms are most likely after short-term treatment with BZs. A review of the literature indicates that 63% to 81% of anxiety-disordered patients will experience relapse of anxiety symptoms after stopping BZ treatment (Noyes et al, 1988). *Rebound symptoms* are a return of the original anxiety symptoms in a more intense form than the patient experienced before BZ treatment. These symptoms are often misdiagnosed as a breakthrough of the original anxiety symptoms (Gold et al., 1995). Although it is difficult to differentiate between rebound and relapse symptoms, rebound symptoms tend to be temporary and have a rapid onset after BZ discontinuation. Finally, *withdrawal symptoms* include novel symptoms, which did not occur before treatment. These symptoms usually disappear within 2 to 4 weeks (Noyes et al., 1988). Examples of these symptoms include confusion, paranoia, muscle cramps, and visual perception difficulties. Severe withdrawal symptoms such as seizures occur in less than 2% of patients attempting BZ discontinuation (Noyes et al., 1988). As discussed previously in reference to tolerance, it is believed that long-term BZ use causes the BZ receptor to shift in the inverse agonist direction (Little, Nutt, & Taylor, 1987). Therefore, when BZ use is discontinued, effects that are the opposite of BZ effects often occur (Stephens & Turski, 1995). This shift is called the “withdrawal shift” (Little, Nutt, & Taylor, 1987).

Discontinuation symptoms differ depending on the pharmacokinetics and pharmacodynamics of the specific BZ that has been used in treatment. Because discontinuation symptoms are more severe after abrupt discontinuation of BZs, they are

more common, and occur sooner, after discontinuation of BZs with short half-lives (Rickels, Schweitzer, Case, & Greenblatt, 1990). Most research indicates that if an individual has been taking a BZ for a long time, or is taking a high dose of the drug, they are more likely to experience discontinuation symptoms (Gold et al., 1995). Potency has also been found to be a predictor of discontinuation symptoms, with high potency BZs more likely to lead to symptoms (Tyrer, 1993). However, other studies have found no effect of BZ potency on discontinuation symptoms (Michelini et al., 1996).

Individual factors have also been found to influence the occurrence of discontinuation symptoms – elderly individuals and individuals with pre-existing mental disorders are more likely to experience discontinuation symptoms (Michelini et al., 1996). Individuals with higher MMPI dependency scores are also more likely to experience discontinuation symptoms (Rickels, DeMartinis, Rynn, & Mandos, 1999). Finally, the experience of physical withdrawal symptoms has been shown to be more severe among individuals who focus on these symptoms and interpret them as unbearable (Hayward, Wardle, & Higgitt, 1989). Such studies suggest that BZ withdrawal effects appear to have a cognitive/psychological component in addition to the physical component.

Dependence. According to the DSM-IV (APA, 1994), substance dependence is defined by both physiological and psychological symptoms. Specifically, physical dependence is characterized by tolerance and withdrawal symptoms, as described above (Busto & Sellers, 1991; DSM-IV; APA, 1994). Most studies of BZ dependence indicate that the physical dependence on BZs follows a negative reinforcement model (Busto & Sellers, 1991). That is, dependence occurs when an individual begins taking a BZ to terminate the distress caused by unpleasant withdrawal symptoms associated with BZ discontinuation,

returning the individual to a normal or stable mood state (Gold et al., 1995). Barbiturate dependence is also mediated by a negative reinforcement model (Wise, 1990). This is in contrast to drugs that are mediated by a positive reinforcement model of dependence, in which a drug (e.g., cocaine) brings a pleasurable feeling to a subject who is in a normal or stable mood state, and the person takes the substance repeatedly to re-gain that pleasurable feeling (Wise, 1988). Interestingly, alcohol dependence can be mediated by both negative and positive reinforcement models (Pihl & Peterson, 1995). Individuals can become physically dependent on BZs after only a few weeks of use (Miller et al., 1998).

Although it is apparent that actual physical dependence can develop as a result of tolerance and withdrawal symptoms, there is also evidence that psychological factors play a role in BZ dependence. In fact, between 18 and 20% of patients have shown “pseudowithdrawal” symptoms when they were falsely led to believe that their BZs had been discontinued (Roth, 1989; Tyrer, Rutherford & Huggett, 1981). Psychological dependence symptoms include impaired judgment and mood lability (DSM-IV; APA, 1994). Individuals with panic disorder are very likely to become dependent on BZs, most likely due to their misinterpretation of the withdrawal symptoms that they experience as symptoms of their anxiety disorder (Michelini, 1996).

In addition, the manner in which the drug has been prescribed is an important predictor of withdrawal and dependence (Roy-Byrne & Cowley, 1990). Individuals are prescribed BZs in two main fashions: “as needed” (p.r.n.) and “regularly scheduled” (Stewart & Westra, 1996). Individuals who take BZs on a p.r.n. basis tend to take the BZs only when they are expecting to feel or actually feeling significant anxiety. Therefore, pill taking becomes linked to stressful circumstances and the anxiety reaction. In addition,

these individuals may experience mild withdrawal and rebound symptoms many times throughout the day. As these symptoms mirror anxiety symptoms, the individual will take another pill, further reinforcing the need for BZs (Roy-Byrne & Cowley, 1990). For these reasons, individuals who are taking BZs on a p.r.n. basis may be more likely to experience withdrawal symptoms and to become dependent on the drug. Therefore, the development of BZ dependence after p.r.n. use appears to be based on the negative reinforcement model in which the BZ is repeatedly taken to minimize or avoid aversive withdrawal symptoms, eventually leading to dependence (Gold et al., 1995). Although the negative reinforcement model of drug abuse appears to be responsible for most BZ dependence, it is likely that that p.r.n. use strengthens this reinforcement and causes it to occur more rapidly (e.g., through more frequent exposure to withdrawal symptoms, and because patient is more likely to experience strong anxiety reduction by virtue of taking the medication when experiencing strong anxiety – creating a stronger negative reinforcement contingency between drug taking and anxiety relief in the p.r.n user).

In a recent study, the prescription practices of psychiatrists and general practitioners were compared, to determine how often p.r.n. use was being prescribed in the treatment of anxiety disorders (Westra & Stewart, in press). The results indicated a significant difference in prescribing practices with a minority (only 21.5%) of psychiatrists recommending exclusive p.r.n. usage, as compared to a majority (54.6%) of general practitioners.

Many suggestions have been made for dealing with the common problem of physical dependence to BZs. Experts have suggested drug holidays and occasional injections of BZ antagonists (Woods & Winger, 1995). However, these ideas have not yet

been tested. In New York State, BZ prescriptions can only be issued on a triplicate-copy prescription form, so that one copy can be forwarded to the Department of Health for monitoring (Woods & Winger, 1995). It appears that this government regulation was successful in controlling BZ prescriptions. In fact, BZ prescriptions were reduced to half of their previous rate within one year, compared to a national reduction level of 5-10% in the rest of the United States (Shader et al., 1991). However, in that same year (1989), prescriptions for intermediate-acting barbiturates and other non-BZ hypnotics (e.g., chloral hydrate) in New York increased by 27% and 87%, respectively, as compared with national decreases of 15% and 13% (Shader et al., 1991). These drugs are thought to be less effective and more dangerous than BZs (Shader et al., 1991). According to Shader et al. (1991) the Triplicate Prescription Program was responsible for almost 30,000 prescriptions for barbiturates that would not have been prescribed without the program in place.

Presently, the recommended procedure for discontinuing BZ treatment is to switch the patient to a longer-acting BZ, and to taper this drug over a long period of time (Roy-Byrne, 1991). For example, a patient taking alprazolam who is wishing to discontinue BZ use might be first switched to clonazepam, and then clonazepam would be gradually tapered over time. Several programs have been developed to help medical practitioners successfully taper their patients' BZs (e.g., Alexander, 1988) and withdrawal symptoms after gradual taper tend to range from "mild to moderate" (Schweitzer, Rickels, Case, & Greenblatt, 1990). However, many patients are still not successful in BZ discontinuation, even with a slow taper program, most likely due to the development of psychological dependence. CBT interventions can also be helpful for patients who are having difficulty

dealing with physical symptoms occurring during BZ withdrawal (Michellini et al., 1996; Otto et al., 1993). In one study, CBT techniques were used to help individuals with panic disorder to discontinue long-term BZ use. Of the patients who completed the 10-session program, 76% were able to discontinue their medication, and maintain a lower level of anxiety symptomatology off the drugs (Otto et al., 1993). Of course, all patients should be educated about withdrawal and rebound symptoms, so that they do not misinterpret these symptoms as returning anxiety symptoms (Spiegel, 1999).

Potential of Benzodiazepines for Addiction and Abuse. There is quite a bit of disagreement in the research literature about the definitions of addiction and dependence (Wise, 1988). As noted by Salzman (1998), the terms “dependence” and “addiction” are incorrectly used and wrongly treated as interchangeable terms. Although one cannot have addiction without dependence, dependence can occur alone (Salzman, 1998). Addiction implies that the patient craves the drug and engages in a pattern of overuse despite adverse consequences (Miller, Gold & Stennie, 1995). Many researchers have noted that most chronic BZ users do not increase their dose or “drug seek” (APA Task Force, 1990). However, this viewpoint may be overly complacent, as chronic BZ users do not have to “drug seek” if they are receiving regular BZ prescriptions from their doctors (Ashton, 1995). Regardless, many other individuals use BZs illicitly. The National Household Survey on Drug Abuse (Woods & Winger, 1995) reported that 1-3% of the population reported non-medical use of BZs in 1992. This rate of illicit use of BZs is similar to the reported rates for heroin, cocaine, or barbiturates (Griffiths, 1995). BZs are usually misused by polydrug users who are also abusing drugs such as cocaine, heroin, or alcohol (Lader, 1995). It is estimated that over 70% of BZ abuse is part of polydrug or alcohol

abuse (Longo, 1998a). Over 30% of individuals entering drug treatment programs report using BZs in the prior year (Brown & Chaitkin, 1981). Usually, these polydrug users are not physically dependent on BZs, but are using them to treat withdrawal effects, and to augment the effects of the illicit drugs. This is consistent with the features of substance abuse, in which an individual is using the drug despite adverse consequences, but is not physically dependent on the drug (i.e., no symptoms of withdrawal or tolerance) (DSM-IV; APA, 1994). Although BZs can be bought on the streets, many addicts have become adept at “role-playing” anxiety symptoms that meet DSM-IV criteria for an anxiety disorder to obtain BZ prescriptions from medical professionals (Longo, 1998a). It has been hypothesized that alcoholics may find BZs more reinforcing than other individuals and may be more likely to abuse BZs. Alcoholics may find BZs particularly reinforcing because they cause some effects that are similar to alcohol, as they both act on the GABA system (Engel & Liljequist, 1983). The fact that alcoholics find BZs reinforcing is highly problematic, as BZs are thought to act synergistically with alcohol (Ashton, 1995) and because anxiety disorders and alcoholism often occur comorbidly (Kushner, Sher, & Beitman, 1990). Ciraulo and Sarid-Segal (1991) found that alcoholics reported higher drug liking scores and improved mood after administration of an acute dose of a BZ, as compared to non-alcoholics. Overall, it appears that BZs with a rapid onset of action (e.g., triazolam, diazepam) are more likely to be abused, as these drugs produce their effects quickly (Ciraulo & Sarid-Segal, 1991).

Interestingly, most research indicates that individuals with anxiety disorders do not find BZs reinforcing when taken under blind conditions (de Wit & Griffiths, 1991; McCracken, deWit, Uhlenhuth, & Johanson, 1990). However, a recent pilot study (4

participants) found that 3 of the 4 participants with GAD chose to self-administer diazepam, as opposed to placebo (Roache & Meisch, 1995). The administration in the latter study occurred p.r.n., which might account for this discrepant finding (Westra & Stewart, in press). Obviously, more research needs to be conducted in this area.

Chapter Summary

BZs are a widely used class of drugs that are effective in the short-term treatment of anxiety, insomnia and other disorders. BZs are much safer and have fewer side effects than drugs that were previously used as anxiolytics and sedatives, such as the barbiturates. However, it is now understood that these drugs have very serious withdrawal effects and can quickly cause physiological dependence, particularly for clinically anxious individuals (the very people for whom BZs are most frequently prescribed). As BZs are effective, and chronic users do not usually escalate their dosage of the drug, one might wonder why long-term users should even attempt to curtail their BZ use (Hayward et al., 1989). As noted by Klerman et al. (1989), many critics of BZs are implicitly subscribing to an “antibiotic model” of drug treatment – that is, they are expecting the drug to continue working or “cure” the disorder, even after pharmacologic intervention is stopped. Alternately, Klerman et al. (1989) feel that a “chronic disease model” is more applicable to anxiety disorders. Like diabetes, epilepsy, and hypertension, individuals with anxiety disorders may have to take BZs for a lifetime. However, one problem with this suggestion is that there are several adverse consequences of BZ use in terms of their impact on aspects of human cognition. Moreover, tolerance does not develop to all of these consequences equally. In the next chapter, I will review the research findings and

controversies regarding the most common effects of BZs on human cognition: sedation, inattention, and amnesia.

Chapter Two

Cognitive and Sedative Effects of Benzodiazepines

Until the 1970s, it was assumed that oral BZs did not have any significant cognitive side effects (Hommer, 1991). However, it is now known that there are several effects of BZ administration upon aspects of human cognition. Common cognitive side effects include sedation and impairment of attention and memory. It should be noted that whether a cognitive effect of a drug is considered a “side effect” depends upon the reason that the BZ has been prescribed. For example, if a BZ is prescribed as a sleeping pill, feelings of sedation are not considered a side-effect, but rather an intended, therapeutic effect. However, if a BZ is prescribed as an anxiolytic, sedation may be a significant problem. In this chapter I will review the research findings and controversies regarding the most common cognitive changes associated with BZ use in humans: sedation, inattention, and amnesia. It should be noted that most of the studies regarding the cognitive effects of BZs investigate the effects of acute doses of BZs in normal participants without a history of BZ or other psychotropic medication use.

Cognitive Impairments Associated With Benzodiazepines

One of the difficulties in investigating cognitive impairments associated with BZ administration is that tasks that are “pure” measures of sedation, attention, or memory are rare or even nonexistent (Fluck et al., 1998). In this chapter I will divide cognitive tasks according to the most salient aspect of cognition thought to be assessed by each. In addition, whenever possible, I will describe the procedures that have been used to determine what cognitive processes are actually being measured by each task.

Sedation

In the 1960s, anaesthesiologists began using BZs as a pre-operative medicant to calm patients before surgical procedures. These anaesthesiologists noted that, in addition to decreased anxiety, patients were reporting increased sedation (Haslett & Dundee, 1968). This sedation was not considered an unwanted side-effect by anaesthesiologists, as it was believed to combine with the drug's anxiolytic effect to keep the patient calm and compliant before the surgical procedure. However, sedation is an unwelcome side effect for individuals taking BZs as a day-time treatment for clinical anxiety.

When assessing the sedative effects of a drug it is important to obtain subjective, observer-rated, and objective measures of sedation. Subjective sedation measures require the participant to use internal or bodily cues (i.e., feeling sleepy) to measure sedation. Subjective measures of sedation require that the participant be aware of changes in their behavior and feelings, and that they correctly interpret these changes (Weingartner, Sirocco, Rawlings, Joyce, & Hommer, 1995). It is possible that a participant may not report being sedated but may show psychomotor slowing on an observer-rated or objective sedation measure. Alternatively, a participant may report feeling sleepy, but this subjective state might not affect their speed in performing cognitive tasks, and might not be observable to others. Observer-rated sedation measures require the experimenter/observer to use information from a participant's outward appearance (e.g., participant appears lethargic) to measure sedation. Observer-rated sedation measures can be prejudiced by factors such as the observers' training or beliefs about the effects of the drug (Green, McElholm, & King, 1996). However, if participants do not rate themselves as significantly sedated, but observer ratings and/or objective sedation ratings suggest

sedation, this would indicate that BZs may be affecting “meta-cognitive processes” or “reflective” functions (Bacon et al., 1998; Weingartner et al., 1995). In other words, such a discrepancy would indicate that BZs may impair users’ abilities to evaluate their own competence.

Subjective Measures of Sedation

To assess subjective sedation in most studies of BZs, participants are usually presented with a series of visual analogue scales (VASs; e.g. alert-drowsy; energetic-lethargic) on which they are asked to rate their current state (e.g., Block & Berchou, 1984). Most commonly, the scales used are derived from a series of VASs created by Bond and Lader (1974) that have been found to reliably measure sedation in drugged participants (Weingartner et al., 1995). Studies using diazepam (Danion, Zimmermann, Willard-Schroeder, Grangé, & Singer, 1989; Eves, Curran, Shine, & Lader, 1988), lorazepam (Curran, Gorenstein, & Lader, 1993b; Curran, Pooviboonsuk, Dalton, & Lader, 1998; Curran, Schifano, & Lader, 1991), flunitrazepam (Pompeia, Gorenstein & Curran, 1996), nitrazepam (Pompeia et al., 1996), and oxazepam (Stewart, Rioux, Connolly, Dunphy, & Teehan, 1996) have almost consistently indicated that participants rate themselves as being more drowsy, more relaxed, or mentally slower after a single clinical dose of a BZ relative to both their own pre-drug sedation levels and to placebo-treated participants. However, one study, using lorazepam, did not find significant effects, although the means were in the expected direction (Bishop & Curran, 1995). However, in this study, the sedation ratings were obtained at a time when participants were aware that they were about to receive a needle. It is probable, as suggested by the

authors, that anticipatory anxiety regarding the injection may have aroused participants, causing them to feel less drowsy.

In another study, healthy participants were asked to provide subjective ratings of the quality of their sleep, speed of awakening, and alertness upon waking, after taking a clinical dose of alprazolam (Allen, Curran, & Lader, 1991). Results indicated that participants believed that the quality of their sleep was improved by BZs compared to placebo-treated participants, but that there was no difference in speed of awakening or feelings of alertness once awake (Allen et al., 1991). This is most likely due to the fact that the effects of the drug would have dissipated by the morning. Taken together, most of these studies indicate that BZs reliably induce subjective feelings of sedation.

Observer-Rated Measures of Sedation

Most studies of BZs do not include observer-rated measures of sedation. However, a few studies in the pediatric anaesthesia literature have used observer-rated sedation measures, most likely because very young children may not be able to accurately report on their own sedation levels. Typically, 4- or 5-point Likert scales are used by examiners to rate sedation. Studies indicate that children who have been administered a BZ (midazolam) before a medical procedure appear significantly more sedated than placebo-treated children (Wilton, Leigh, Rosen, & Pandit, 1988; Weldon, Watcha, & White, 1992). However, these studies are confounded by the possibility of increased anxiety in children who had not received the anxiolytic. Obviously, an unmedicated child who is crying due to pre-operative anxiety is not going to be observer-rated as calm or asleep, therefore merely appearing less “sedated” than the BZ-treated child.

Objective Measures of Sedation (i.e., Psychomotor Speed Measures)

To objectively measure sedation, researchers usually present participants with one of many behavioural tasks that measure their response speed. The most commonly used task is the Digit Symbol Substitution Task (DSST) from the Wechsler Adult Intelligence Scale (Wechsler, 1981). This has been found to be a reliable measure of sedation in both drugged and non-drugged participants (Weingartner et al., 1995). In this task, participants are required to learn a code in which symbols are paired with the digits 1 through 9. Participants are asked to copy the symbols associated with each digit, in the order presented, as quickly and accurately as possible. The DSST is scored as the total number of symbols correctly substituted for digits in a 90 second period. Although usually given as a paper and pencil task, the test has also been administered in computerized form (Ellinwood, Heatherly, Nikaido, Bjornsson, & Kilts, 1985).

Consistently, results of studies using the DSST indicate that clinical doses of BZs such as oxazepam (Curran et al., 1993b; Curran, Schiwy, & Lader, 1987b), lorazepam (Curran, Allen, & Lader, 1987a; Curran et al., 1991; Curran et al., 1993b; Curran et al., 1998), and diazepam (Danion et al., 1990; Fang, Hinrichs, & Ghoneim, 1987) slow performance compared to a placebo-treated group. When attentional performance (see next section) is covaried out, BZ-induced impairments still remain on the DSST (Curran et al., 1987b). The relationship between performance on the DSST and subjective measures of sedation is significant for high doses of triazolam ($r = -.73$ to $-.54$, depending on time [post-drug administration] sedation is tested), but is non-significant for moderate or low doses (Weingartner et al., 1995). This finding suggests greater correspondence between objective and subjective sedation measures at higher BZ doses.

One difficulty with the DSST is that the task does not strictly measure sedation. The task also has a large memory component. In addition to assessing psychomotor speed in replacing the symbols with numerals, performance on the task can typically be facilitated when the participant memorizes the 9 symbol-digit pairs. However, memory is another cognitive function that is impaired by BZs (see later section). In contrast, the Symbol Copying Test (SCT) requires participants to copy a series of symbols, but they do not have to remember a code. Studies have found that participants who have taken a clinical dose of lorazepam (Curran et al., 1987a; Curran et al., 1991; Curran et al., 1998) or oxazepam (Curran et al., 1987b) are significantly slowed compared to placebo participants on the SCT. However, in another study, the pattern of results was similar, but the effect was not statistically significant after a clinical dose of diazepam (Boulenger et al., 1989). Although the SCT does not have a memory component, it may still be confounded by BZ-induced attentional impairments. However, when attentional performance is covaried out, the BZ-induced differences on the SCT remain significant (Curran et al., 1987b).

Another task that measures psychomotor speed is the Discriminant Reaction Time Task (DRTT). In this test, participants look at a computer screen on which a series of digits are flashed (Block & Berchou, 1984). The participants are instructed to press a button whenever a target digit (e.g., 3) is flashed. The flashing of the digits slows or accelerates depending on the correctness and speed of the participant's responses. The mean time between digits being flashed is used as a measure of the participant's response speed. Results indicate that after a clinical dose of alprazolam or lorazepam, BZs slow response speed, compared to placebo-treated participants on the DRTT (Block &

Berchou, 1984). However, this task has an attentional component and the results of the Block and Berchou (1984) study might be due to attentional impairments, as opposed to increased sedation.

Other objective measures of sedation have assessed psychomotor speed, as opposed to cognitive processing speed. The Finger Tapping Test uses a finger tapping mechanism to measure how many times a participant can tap in a specific amount of time (usually 60 seconds). Although most studies indicate that finger tapping speed is slowed compared to placebo-treated participants after administration of a clinical dose of diazepam (Fang et al., 1987), oxazepam (Curran & Gorenstein, 1993; Curran et al., 1993b), or lorazepam (Bishop & Curran, 1995; Bishop, Curran, & Lader, 1996; Curran & Gorenstein, 1993; Curran et al., 1993b; Curran et al., 1991; Curran et al., 1998), other studies using lorazepam (Curran et al., 1987a; Preston, Ward, Broks, Traub, & Stahl, 1989) failed to find a significant difference. It should be cautioned, however, that this objective measure of sedation is usually considered to be influenced by motivational factors as well as arousal, and thus the Finger Tapping Test cannot be considered a “pure” measure of psychomotor speed.

As noted above, most measures of objective sedation are confounded by other factors such as attention, subjective sedation, motivational, and memory requirements (Green et al., 1996). To deal with these problems, measures of saccadic eye movements have been used as an alternative objective measure of sedation. Saccadic eye movements are rapid eye movements that occur when a participant quickly shifts his or her gaze from one target to a second target. Research has shown that the velocity of these movements cannot be consciously changed (Green et al., 1996). Therefore, this may be a more

“pure” measure of objective sedation (Green et al., 1996). Although rarely used, research indicates that peak saccadic velocity is significantly slowed after administration of clinical doses (1 or 2 mg) of lorazepam (Green et al., 1996). This objective measure has been shown to be significantly correlated with a subjective measure of sedation (VAS: $r = -.36$) (Green et al., 1996).

An additional physiological measure of objective sedation that has been used in studies of benzodiazepines is the Critical Flicker Fusion Threshold (CFFT) which is believed to be a measure of central nervous system arousal (Curran et al., 1998). In this task participants use one eye to view a flickering light. The frequency of the flicker is first increased until the participant indicates that the flicker has disappeared. Next, the frequency of the flicker is decreased until the participant is again able to detect a flicker. Typically, participants are administered a series of ascending and descending trials. Next, detection threshold on both the ascending and descending CFFT trials are combined to create a total CFFT performance score. Researchers have found that ability to detect flicker changes on the CFFT (i.e., total performance score) is impaired by a clinical dose of lorazepam (Curran et al., 1998; Preston et al., 1989). In addition, long-term users of BZs also showed impaired performance on the CFFT (Lucki, Rickels, & Geller, 1986).

Summary of Effects of BZs on Sedation Measures

It appears that BZs induce high levels of subjective sedation in participants after a single, acute dose. After administration of a BZ, participants are slowed on objective sedation measures (cognitive processing speed and psychomotor speed tasks). These effects are found across various BZs and when confounding variables of memory and

attentional requirements of the paradigms are controlled. Although these objective and subjective measures of sedation are significantly correlated, the correlations are not strong enough to recommend using only one measure exclusively (Green et al., 1996). In fact, one study indicated that after administration of different doses of triazolam, participants showed dose-dependent impairment on objective measures of sedation, but the same participants were not able to differentiate between the doses on subjective measures of sedation (Weingartner et al., 1995).

In a recent study, participants who had taken a mildly sedative dose (2.5 mg) of lorazepam were compared to sleep deprived individuals (problem snorers and on-call doctors). It was found that the BZ group became sleepier as the cognitive testing progressed, while the sleep-deprived participants became more alert (Fluck et al., 1998). Therefore, it appears that it is difficult, if not impossible, to overcome the sedation associated with an acute dose of a BZ (Fluck et al., 1998). The sedative effects of BZs have been found to contribute to traffic accidents and workplace injuries. In addition, BZs have been found to contribute to increased risk of falls and hip fractures in the elderly (Kirby et al., 1999). Therefore, it is essential that patients be advised of this impairment before they begin taking BZs (Ashton, 1995). This is especially true for elderly patients, for whom BZ-induced sedative effects last longer and are more severe (Ashton, 1995). It should be noted that the sedative effects of BZs are subject to tolerance with repeated dose administration. Tolerance to the various cognitive effects of BZs is discussed at the end of this chapter.

Attention

The effects of BZs on attentional processes are not as widely studied as the effects of BZs in inducing sedation. Obviously, it is important to study the effects of BZs on attention, as attentional abilities are important for many aspects of day-to-day functioning. A difficulty with the assessment of attention is that the concept of attention is multidimensional (Ewing-Cobbs et al., 1998). Attention cannot be reduced to a unitary description, and cannot be assessed using a single test (VanZomeran & Brouwer, 1994). In addition, there are differences in the nomenclature used by theorists when describing the components of attention that are being measured by a certain task (Ewing-Cobbs et al., 1998). Mirsky, Anthony, Duncan, Ahearn, and Kellam (1991) conducted a principal components analysis on many commonly used attention tasks in an attempt to create an empirically-derived model for conceptualizing the components of attention. Their research indicates a four-factor model of attention composed of focus/execute, sustain, encode, and shift elements. The empirical distinction between these four elements of attention appears to be supported by parallel activation of different regions of the brain (Mirsky et al., 1991). The focus/execute element measures a participant's ability to direct attention to stimuli, or to select target stimuli from an array. The sustain element measures a participant's ability to maintain focus/attention over time. The encode element measures a participant's ability to perform mental manipulation tasks. The element of shifting attention is the ability to switch attention between stimuli, channels and tasks. In addition to Mirsky et al.'s four elements, researchers also measure divided attention, or the ability to perform two or more tasks at the same time (Stankov, 1983). Although it is helpful to investigate these various elements of attention separately,

attentional tasks usually measure more than one attentional process. For review purposes, I have attempted to divide various attention tasks based on their most salient attentional demands.

1) Focus/Execute Attention Tasks

Results of investigations using a variety of BZs converge in finding that BZs interfere with the focus/execute function of attention. The most commonly used paradigms are symbol, digit, or letter cancellation tasks. In these tasks, participants are required to search for and cross out targets (e.g., the number 4) from a sheet of random symbols, digits, or letters. In most studies, a total score is created by combining the time taken to complete the task with omission and commission errors (Curran et al., 1991; Curran et al., 1993b). Results indicate that performance on this task is impaired, compared to placebo-treated participants, by administration of a clinical dose of diazepam (Fang et al., 1987; Vidailhet et al., 1994; Vidailhet, Kazès, Danion, Kauffmann-Muller, & Grangé, 1996) or lorazepam (Bishop & Curran, 1995; Curran et al., 1991; Curran et al., 1993b; Vidailhet et al., 1994; Vidailhet et al., 1996). However, another study using lorazepam failed to find a significant difference (Curran et al., 1998). Interestingly, one study found that covarying tapping speed left no significant lorazepam treatment effects on the Digit Cancellation Task (Curran et al., 1993b) suggesting that lorazepam's sedative effects may contribute to apparent "attentional" impairments on cancellation tasks.

2) Sustain Attention Tasks

This attentional element has typically been assessed using the List Repetition Task. Like focused attention paradigms, these studies have also found performance to be

impaired following BZ administration. The List Repetition Task requires participants to listen to a list of categorically related words, half of which are presented twice.

Participants are instructed to indicate whenever they hear a repeated word. Performance on this task is impaired by administration of a clinical dose of triazolam (Weingartner, Hommer, Lister, Thompson, & Wolkowitz, 1992), diazepam (Hommer, Weingartner, & Breier, 1993), and alprazolam (Fleishaker, Garzone, Chambers, Sirocco, & Weingartner, 1995), relative to placebo treated participants.

3) Encode Attention Tasks

Again, using a variety of different BZs and paradigms, studies assessing the encoding function of attention further support attentional impairments with BZs. In the Paced Auditory Serial Addition Task, participants are presented with pairs of single digit numbers read at increasing speed. Participants are required to add the digits and respond before the next numbers are read. Results indicate that participants who have taken a mildly sedative dose (2.5 mg) of lorazepam are impaired, relative to placebo-treated participants, when responding on this task (Fluck et al., 1998). Similarly, in the Mental Arithmetic Task, participants are required to serially subtract 7's from a three-digit number. Results using this task indicate that lorazepam-treated participants show impaired performance, as compared to placebo-treated participants (Curran et al., 1987a).

In another encode task, the participant is asked to listen to groups of "bleeps" from a computer. At the end of each set, the participant is asked how many bleeps they counted. Results indicate that participants who have taken a clinical dose of lorazepam display more errors on this task relative to placebo-treated participants (Preston, Ward, Broks, Traub, & Stahl, 1989).

4) Shift Attention Tasks

Although few studies investigating attentional shifting have been conducted, two studies, using triazolam, indicate that BZs do have an effect on an individual's ability to shift attention. Attention researchers have noted that shifts of attention can be controlled either voluntarily (i.e., endogenously) or involuntarily (i.e., exogenously) (e.g., Wright & Ward, 1994). These two processes have also been referred to as "controlled" and "automatic" attention allocation processes, respectively. With respect to involuntary or automatic attentional orienting, visual attention can be "captured" by the sudden onset of a stimulus (i.e., an "exogenous" stimulus) in the periphery. In contrast, voluntary or controlled attentional orienting involves the individual making a voluntary, conscious decision to shift attention to a particular position in space using internal ("endogenous") cognitive processes (see review by Klein, Kingstone, & Pontefarct, 1992). Both types of attentional shifts function to enhance processing of visual information at that specific position in space (e.g., Posner, 1980; Posner, Nissen, & Ogden, 1978; Posner, Snyder, & Davidson, 1980). These two types of attentional orienting are typically studied using Posner's cued visual orienting paradigm (Posner et al., 1978).

In this paradigm, participants are often asked to search for and respond to a visual "target" (e.g., a letter). Their task may involve simple target detection or a choice speeded response. On each trial, a visual "cue" is presented prior to the target. This cue can vary in terms of its "informational value" and "type". In terms of informational value, the cues can provide one of three kinds of information about the future location of the visual target. In the uninformative cue condition, if there are two target locations, the target will occur at the cued location 50% of the time (and at the uncued location the

other 50% of the time). In the informative cue condition, the participant can use the cues to predict where the target will be presented on the majority of trials (e.g., 75% valid; 25% invalid). In the neutral condition, no location cueing occurs. In terms of cue type, the cue may appear at a central location (i.e., endogenous cue) requiring the participant to make a voluntary decision to shift attention to the cued location. Informational cues in the endogenous (central) cue paradigm typically consist of an arrow pointing to the target location, whereas neutral cues typically consist of a plus sign. Moreover, central cues (in the endogenous cue paradigm) are usually informative so the participant can use them to predict where the target will be presented the majority of the time (e.g., 75% valid; 25% invalid). As such, this paradigm is purely “endogenous”, requiring the participant to make a conscious decision to shift attention to the cued position in space using internal cognitive processes. Alternatively, the cue may appear at a peripheral location (i.e., exogenous cue), automatically capturing the participant’s visual attention and drawing it toward the cued location. The informational cue typically consists of a visual cue occurring at the target location. If there are two possible locations, a neutral cue could consist of visual cues occurring at both possible target locations simultaneously.

Although the peripheral cue paradigm is designed to assess exogenous shifts of attention, peripheral cueing is purely exogenous only when the peripheral cues are uninformative. In other words, since cues predict the correct target location on only 50% of trials, any shifts of attention toward the cue location must be automatic rather than the result of a strategic, conscious decision to shift attention to the cued spatial location. In contrast, the peripheral cue paradigm assess a mixture of both exogenous and endogenous orienting

when the peripheral cue tells the participant with greater than chance probability where the target will occur (e.g., 75% valid; 25% invalid).

In both the endogenous and exogenous cueing paradigms, the effects of informational cues are typically measured by conducting “cost - benefit” analyses involving three types of comparisons. First, the difference between reaction time (RT) for the valid versus neutral trials is termed “benefits”. Second, the difference between RT for the invalid versus neutral trials is termed “costs”. Finally, the difference between RT for the valid versus invalid trials is termed “costs plus benefits” (Posner et al., 1980). Benefits refer to the RT advantage or facilitation conferred by having available correct information as to target location prior to target presentation. This allows target stimuli to be detected more quickly at the attended location relative to non-attended locations (Posner & Snyder, 1975). Benefits are thought to result from the shift and engagement of attention to the correct spatial location prior to target onset (Wright, Burns, Geffen, & Geffen, 1990). The automatic facilitation effect or benefit seen with exogenous cueing has been referred to as an “attentional grasp reflex” (Maruff & Currie, 1995). Costs refer to the reaction time disadvantage conferred by having one’s attention shifted to an incorrect spatial location prior to target presentation. Costs are thought to result from the shift and engagement of attention to an incorrect spatial location, and then having to disengage attention from the incorrect location, shift and re-engage attention to the correct target location (Clark, Geffen, & Geffen, 1989). Costs plus benefits (Jonides & Mack, 1984; Posner, 1986) represent a composite measure of the time required for all of these various components involved in the orienting of visual attention.

Johnson, Weingartner, Andreason, and George (1995) used a version of Posner's cued visual orienting paradigm to examine the effects of a BZ (i.e., triazolam) vs. placebo on visual attentional orienting. Two types of cues were utilized (central and peripheral) to assess the effects of triazolam on controlled and automatic attention allocation mechanisms, respectively. In addition, in both the central and peripheral cue conditions, cues were informative such that participants could use them to predict where the target would occur on the majority of trials (i.e., 75% valid, 25% invalid). A main effect of drug condition was observed such that RT was slowed overall for triazolam compared to placebo. As described previously, this drug group main effect might reflect sedation rather than attentional impairment, per se. Drug condition did not interact with cue type (central vs. peripheral). Rather, RTs following both exogenous and endogenous cues were slowed by triazolam compared to placebo. Also, the critical three-way interaction (i.e., cue validity x cue type x drug condition) required for demonstrating a dissociation between endogenous and exogenous orienting was not significant. However, drug condition did interact with cue validity. Specifically, the costs plus benefits were significantly greater for triazolam than for placebo. The authors interpreted this finding to suggest that triazolam selectively impairs attentional disengagement and/or attention shifting mechanisms, and that this drug effect is not different for endogenous versus exogenous attentional processes. However, the authors' failure to include a neutral cue condition complicates the interpretation of these findings with respect to which particular aspects of visual attentional orienting are impaired by triazolam, as the authors were unable to calculate separate "costs" and "benefits". Moreover, their peripheral cue condition used informative cues (75% valid; 25% invalid) thus tapping a mixture of

exogenous and endogenous orienting rather than purely exogenous processes. Thus, it may be premature to conclude that triazolam does not selectively impair endogenous versus exogenous orienting on the basis of the results of the Johnson et al. (1995) study alone.

A later study by Carter, Maddock, Chaderjian, and Post (1998) was designed to replicate and extend the findings of Johnson et al. (1995). Like Johnson et al. (1995), Carter et al. (1998) also used versions of Posner's visual orienting paradigm to examine the effects of triazolam on controlled and automatic attentional allocation mechanisms. However, Carter et al. (1998) felt that there were a number of methodological limitations to the Johnson et al. (1995) study and they made alterations to the paradigm accordingly. For example, by including a neutral cue condition in addition to the valid and invalid cue trials in both the peripheral and central cue paradigms, Carter et al. (1998) were able to separately examine drug effects on each aspect of visual attentional orienting. In addition, given the problems with Johnson et al.'s (1995) peripheral cue paradigm, Carter et al. (1998) changed the informational value of the peripheral cues to have no utility in predicting the future location of targets (i.e., 50% valid; 50% invalid) so as to tap purely exogenous attentional processes. Finally, Carter et al. (1998) examined participants' performance at two separate cue-to-target intervals (i.e., stimulus onset asynchronies; SOAs - 150 and 800 ms), in contrast to Johnson et al. (1995) who examined only the shorter of these SOAs.

In this study, which used a peripheral cue paradigm that tapped purely exogenous processes, triazolam selectively modified performance on automatic orienting to exogenous cues at the shorter SOA. Specifically, the benefits of valid cueing in the

peripheral cue paradigm were greater for triazolam than for placebo. The authors interpreted this finding to suggest that triazolam might lead to an increase in facilitation and/or a reduction in inhibition for automatic attentional orienting mechanisms. With respect to increased facilitation, the findings suggest that the attentional grasp reflex may be enhanced with triazolam, as has been shown with aging and with Alzheimer's disease (Maruff & Currie, 1995).

Thus, there are some consistencies and some inconsistencies between the results of the Johnson et al. (1995) and the Carter et al. (1998) studies. In terms of similarities, both found attentional changes with triazolam at the shorter SOA and both found attentional changes with triazolam for the exogenous cueing paradigm, although Johnson's study did not use a purely exogenous task. Carter et al.'s (1998) findings of greater RT benefits with triazolam are consistent with Johnson et al.'s (1995) greater costs plus benefits for triazolam (i.e., the greater costs plus benefits in the latter study may have been entirely attributable to increased benefits). However, the studies differed in terms of whether drug induced attentional changes were specific to automatic attentional mechanisms (Carter et al., 1998) or more general to both automatic and controlled attentional processes (Johnson et al., 1995). This discrepancy may be due to changes in the paradigm (e.g., % of pre-cues that were valid) and/or to differences in the dose of triazolam used (i.e., a lower dose was used by Carter et al. [1998]) across the studies. Finally, Carter et al.'s claim that triazolam leads to greater facilitation and/or decreased inhibition (i.e., increased benefits) on the exogenous cueing paradigm must be interpreted cautiously. A closer examination of their data indicates that their neutral cue condition did not always "behave" as would be expected. In fact, at the shorter SOA for

the exogenous cue paradigm, the placebo group did not just show less RT benefits than triazolam. In fact, placebo-treated subjects showed no benefits whatsoever since neutral pre-cues were associated with faster (rather than slower) RT compared with valid cues. Many researchers have noted similar problems with the neutral cue condition leading some to suggest abandoning its use altogether (e.g., Jonides & Mack, 1984; Posner, 1986) as was the case in the Johnson et al. (1995) study.

Taken together, these two studies clearly suggest that BZs do affect attentional shift functions. However, which particular aspects of visual attention allocation mechanisms are implicated (e.g., shift, engage, disengage, re-engage) remains unclear. Further research is also needed on whether BZ effects on this component of attention are limited to automatic attention allocation processes (as is suggested by the preliminary work of Carter et al., 1995) or whether they are generalizable to both automatic and controlled attention allocation processes (as suggested by the preliminary work of Johnson et al., 1998).

5) Divided Attention Tasks

Few studies have investigated BZ effects on divided attention. A recent study examined the effect of dividing attention of participants who had taken a clinical dose of diazepam (Gorissen & Eling, 1998). Participants were required to learn word pairs in a single task condition, and then to learn word pairs at the same time as performing a visual discrimination task. Overall, dividing attention did reduce the learning of unrelated word pairs, and the BZ group was impaired overall in the learning of unrelated word pairs relative to placebo-treated participants. However, the learning in the BZ group was not

disproportionately reduced compared to the placebo group under the divided attention condition, suggesting that BZs do not impair divided attention (Gorissen & Eling, 1998).

Summary of BZ Effects on Attentional Tasks

Overall, it appears that BZs impair most aspects of attention, with the possible exception of divided attention. The research on shifting attention is not conclusive (Carter et al., 1998; Johnson et al., 1995). Johnson et al. (1995) suggest that attentional shifting is impaired by triazolam. However, Carter et al. (1998), suggest that the automatic attentional shift reflex is facilitated by triazolam. Obviously, more research is needed in this area. The results of one study indicate that divided attention is not impaired by BZs (Gorissen & Eling, 1998). However, divided attention is a very complex cognitive function that is also very difficult for non-drugged participants. Therefore, it is possible that a floor effect may have occurred on the task (Gorissen & Eling, 1998). Further studies are necessary in this area. Findings of impairment across various cognitive paradigms used to assess different aspects of attention highlight the robustness of BZ effects on attentional processes. However, it should be noted that the attentional effects of BZs are subject to tolerance with repeated dose administration, as opposed to some other cognitive effects of BZs that do not appear to be subject to tolerance. Tolerance to the various cognitive effects of BZs is discussed at the end of the chapter.

Memory

A large number of studies have been conducted which investigate the effects of BZs on memory. The amnesia associated with BZ use is an important area of study for many reasons. First, there is little doubt that memory is the most important human

cognitive ability (Ghoneim & Mewaldt, 1990). Obviously, memory impairments would be highly detrimental to a person's day-to-day functioning. Therefore, it is important to determine what aspects of memory are affected by BZs, and how long lasting these effects are.

In addition to understanding the effects of BZs on an individual's memory functioning, researchers are also attempting to determine if BZ-induced amnesia is similar to organic amnesia (Brown, Lewis, Brown, Horn, & Bowes, 1982; Ghoneim & Mewaldt, 1990). If the two forms of amnesia are indeed similar, this could lead to significant advances in the understanding of organic amnesia. Research in this area could proceed much more quickly since researchers could use BZs to induce a temporary amnesia rather than having to recruit clinical participants with organic amnesia. Moreover, by using BZs to create the experimental amnesia group, it would be much simpler for researchers to obtain comparable groups of amnesiacs and controls. In fact, participants would be able to act as their own controls (Hirshman, Passanante, & Arndt, 1999).

Researchers also study the effects of BZ treatment on memory with the purpose of determining if BZs differentially affect the various types of memory processes suggested by memory theorists. This research can assist in determining if theoretically distinct memory systems are, in fact, empirically separable memory processes (Hirshman et al., 1999).

Finally, research on BZs and memory may have important clinical implications for the many individuals who take these medications for therapeutic purposes. Approximately 60% of panic disorder patients that seek treatment from a psychotherapist

are taking an anxiolytic, most often BZs (Otto, Pollack, Penava, & Zucker, 1999). If these drugs are affecting memory, it is possible that these individuals may not remember the material they are being exposed to through therapy. Recent naturalistic research indirectly supports this hypothesis, and indicates that BZs taken concurrently with psychotherapy may have a detrimental effect on CBT outcome in the treatment of anxiety disorders (Westra & Stewart, 1998; Westra, Stewart, & Conrad, in press).

Types of Memory

As reviewed by Ghoneim and Mewaldt (1990), research indicates that memory is not a unitary concept. Although many different models of memory functioning exist, some memory theorists have described three basic types of memory: sensory memory, short-term memory, and long-term memory (e.g., Atkinson & Shiffrin, 1968).

Sensory Memory. Sensory memory contains brief sensory impressions that remain after a stimulus is no longer present (Atkinson & Shiffrin, 1971). This memory process occurs automatically, without voluntary control. According to a review by Ghoneim and Mewaldt (1990), there are no studies of the effects of BZs on sensory memory.

Short-Term Memory. Short-term memory occurs when an individual actively attends to a stimulus. The capacity of short-term memory is small, and if the memory is not actively rehearsed, it will be quickly forgotten (Murdock, 1971). Studies using the Digit Span Test have found that short-term memory is not impaired, relative to placebo-treated participants, by a clinical dose of oxazepam (Curran et al., 1987b), lorazepam (Bishop et al., 1996; Curran et al., 1987b; Curran et al., 1991; Sellal et al., 1992), or diazepam (Eves et al., 1988; Sellal et al., 1992). In addition, participants who have taken BZs still show a “recency effect” (better memory for words shown at the end of an encoding list) when

recalling a previously-presented word list, providing further evidence that short-term memory remains intact (Curran et al., 1987b).

Long-Term Memory. Long-term memory contains large amounts of information. This information remains in our long-term memory indefinitely without active effort (Atkinson & Shiffrin, 1971). This is the most commonly studied type of memory.

Although much research suggests that long-term memory is impaired by BZ administration, studies have consistently indicated that BZs only impair memory for information acquired after administration of the drug (i.e., anterograde amnesia). No well-designed study has found evidence of amnesia for information acquired before BZ administration (i.e., retrograde amnesia) (Curran, 1986). Information that was presented after BZ administration is not well remembered, even when the drug has been cleared from the body. However, once the drug has been eliminated from the body, there is no amnesia for new information (Curran, 1986).

Interestingly, several researchers have noted an effect opposite to retrograde amnesia on explicit memory tasks assessing memory for material presented prior to BZ administration. BZ-treated participants appear to remember more words from a list presented before drug administration, when compared to placebo-treated participants. This “retrograde facilitation” effect is only apparent if a different word list is presented after drug administration than the list presented prior to drug administration (Curran, 1986). In one study (Weingartner et al., 1995), placebo participants remembered approximately 60% of the pre-drug word list and about 60% of the post-drug word list. In contrast, participants who had received a clinical dose of triazolam remembered approximately 80% of the pre-drug word list and only 30% of the post-drug list. This

retrograde facilitation may be due to the fact that the BZ-treated participants' learning of the post-drug list is less likely to interfere with memory for the pre-drug list due to post-drug memory impairments in learning of the post-drug list (Hinrichs, Mewaldt, Ghoneim, & Berie, 1982).

Long-Term Memory: Explicit and Implicit Memory

Within the construct of long-term memory, researchers commonly distinguish between two main memory processes: implicit and explicit memory (e.g. Graf & Schacter, 1985). Explicit memory occurs when a participant is aware that his or her memory is being tested, and is consciously and effortfully attempting to remember a previous experience. This is the most commonly studied aspect of memory. In contrast, implicit memory occurs when a participant's ability to perform a task is facilitated by a previous experience. Unlike explicit memory, implicit memory occurs without conscious awareness; the individual is unaware that his/her memory is being tested and does not consciously or effortfully attempt to remember his/her previous experience (Graf & Schacter, 1985).

Implicit and explicit memory processes are dissociated by a number of factors including organic amnesia (Squire, Shimamura, & Graf, 1987), Alzheimer's disease (Keane, Gabrieli, Fennema, Growdon, & Corkin, 1991), anticholinergic drugs (Kopelman & Corn, 1988), divided attention (Rabinowitz, Craik, & Ackerman, 1982) and alcohol (Lister, Gorenstein, Risher-Flowers, Weingartner, & Eckardt, 1991). In all of these cases, explicit memory is impaired while implicit memory is spared. Although it is rare to find instances where implicit memory is impaired while explicit memory remains intact, a literature review (Roediger & McDermott, 1993) indicates that altering certain

physical aspects (e.g., typography) of the memory stimuli between the encoding and memory testing phases impairs only implicit memory. This double dissociation lends support to the hypothesis that implicit and explicit memory are qualitatively distinct memory processes that are supported by separate memory systems (Schacter, 1994).

Explicit Memory. Examples of paradigms used to assess explicit memory include free recall, cued recall, and recognition memory tasks. The most common method of assessing explicit memory is to present participants with a list of words (after the BZ has been administered) and to later test their memory for items from the list. Consistently, free recall studies indicate that participants who have received a clinical dose of diazepam (Eves et al., 1988; Legrand et al., 1995), lorazepam (Curran et al., 1987a; Legrand et al., 1995) or triazolam (Weingartner, Rawlings, George, & Eckardt, 1998) are impaired, relative to placebo-treated participants, in their ability to remember word lists. Further analysis of the words remembered indicates that BZs do not affect recall of the last block of words presented (i.e., recency effect) but do impair recall of the first block of words (i.e., primacy effect) (Curran et al., 1987a). This finding is most likely explained by the fact that BZs do not impair short-term memory, as the free recall task in the Curran et al. (1987a) study was given immediately after the word list was encoded. Studies have also found impaired explicit memory in lorazepam (Bishop & Curran, 1995; Stewart et al., 1996) and oxazepam-treated participants (Stewart et al., 1996), using a cued recall task. In a cued recall task, subject's memory of a word list is "cued" by presenting them with a reminder of the words (usually a word-stem). In one study that failed to find an effect of flunitrazepam and nitrazepam on cued recall, the cued recall task only used 10 words and may have been too easy for the participants, creating a

ceiling effect (Pompeia et al., 1996). Several studies have also found impaired recognition, relative to placebo-treated participants, after BZ administration (Bishop & Curran, 1995; Curran, Gardiner, Java, & Allen, 1993a; Curran, Schiwy, Eves, Shine, & Lader, 1988; Weingartner et al., 1998). However, other studies have found no impairment in recognition memory (Eves et al., 1988). Another study only noted recognition impairments for higher doses of BZs (Weingartner et al., 1992). This pattern of results is most likely explained by the fact that recognition tasks place fewer cognitive demands on a participant and are, therefore, less sensitive to drug-induced memory deficits than relatively more taxing free recall tasks (Curran, 1986).

Paradigms using recall of short stories or news items have also demonstrated that participants show impaired ability to remember the details of a story, relative to the placebo group, after receiving a clinical dose of lorazepam (Curran et al., 1987b; Bishop et al., 1996), oxazepam (Curran et al., 1987b) or diazepam (Gorissen, Curran, & Eling, 1998). Similarly, performance on a memory task using a series of pictures as stimuli is impaired, relative to placebo-treated participants, by a clinical dose of diazepam (Eves et al., 1988) or lorazepam (Legrand et al., 1995).

Explicit Memory: Episodic versus Semantic Memory. Within the domain of explicit memory, researchers often distinguish between episodic and semantic explicit memory (Tulving, 1983). Semantic memory is concerned with stored knowledge about language, rules and the world and does not have to be remembered with reference to a particular context (Curran, 1991). In contrast, episodic memory is the memory for a sequence of occurrences (Hommer, 1991), or personally experienced events (Curran, 1991). Episodic memory is the most commonly assessed type of explicit memory. Episodic memory

tasks include all tasks described above (recall and recognition of words, stories, and pictures); performance on these tasks appears to be consistently impaired by BZs. To test semantic memory, participants are usually asked to generate lists of words that fall into a particular semantic category (e.g., large animals). Consistently, results indicate that BZs do not impair semantic memory (e.g. Fluck et al., 1998).

In summary, results of studies using different BZs and different paradigms consistently indicate that long-term explicit episodic memory is impaired by BZs. Interestingly, studies of meta-memory in participants who have taken a BZ indicate that participants are relatively unaware of these memory impairments. In fact, when asked to rate their “feeling of knowing” regarding their answers on an explicit memory test, participants who had taken a clinical dose of lorazepam performed at chance levels, showing that they were not good at identifying which items were correctly remembered and which were not (Bacon et al., 1998). Analysis of their performance on the memory tasks indicated that their performance was impaired. The results of this study indicate that BZ-treated individuals may not be aware that their performance is impaired on a test of explicit memory. It appears that if an individual does not remember anything, he/she may conclude that nothing worth remembering has occurred (Hommer, 1991). Lending support to this explanation, most BZ-treated patients do not complain about memory problems (Barbee, 1993). This lack of awareness of memory impairments has serious implications for individuals who are regularly taking BZs for the treatment of clinical anxiety, as they may not be aware of the detrimental effect of the drug on their daily functioning and may not bring it to the attention of their prescribing physicians. However, other studies have found that when participants who had taken a clinical dose

of lorazepam or oxazepam were asked to remember the details of a story, as opposed to a word list, they were aware that their memory was impaired (Curran et al., 1987b; Curran et al., 1993b). Perhaps, BZ-treated individuals are more aware of memory deficits when the memory task being used more closely simulates real-world memory demands.

Research has also been conducted to determine what stage(s) of memory processing is/are impaired by BZs. Researchers talk about three stages in remembering information: encoding/acquisition, storage, and retrieval (see review by Murdock & Anderson, 1975). First an individual must acquire or encode the information. Secondly, the individual must store this information for later use. Finally, when needed, the individual must be able to retrieve the memory from storage. If BZs interfere with any of these three stages, information will not be remembered (Ghoneim & Mewaldt, 1990). The present view is that it is the acquisition of new information, rather than storage or retrieval that is affected by BZs (Gorissen, Curran, & Eling, 1998). However, it is still unclear which encoding operations involved in memory acquisition are impaired by BZs (Gorissen & Eling, 1998). Several studies have indicated that the encoding of contextual information may be impaired (Brown & Brown, 1990; Curran et al., 1993a). Obviously, memory for an event is influenced by a person's ability to remember where and when the information was encoded (i.e., the context). If a person did not encode contextual information when they went grocery shopping, for example, they might buy the groceries that they had needed the last time they went shopping, instead of those they needed on the present trip. Brown and Brown (1990) presented participants with a word list to be encoded, followed by two recognition memory tasks. Their results indicated that lorazepam-treated participants had more false alarm errors on the second recognition task

than the placebo treated participants. This was because participants were more likely to believe that distractor words used in the first recognition task were words from the encoding task, indicating a deficit in contextual memory. Likewise, Curran et al. (1993a) also found that lorazepam increased the number of prior list intrusions on a delayed recall task. Another study indicated that BZs impair the formation of new associations, such as the association between target and contextual information (Gorissen et al, 1988).

Implicit Memory. The paradigms that are most commonly used to investigate implicit memory are “priming” tasks such as the word-stem completion task and the picture-fragment completion task (see review by Roediger & McDermott, 1993). In the word-stem completion task, participants encode a word list and are later asked to complete a series of three letter word stems with words that come to mind. Typically, participants are more likely to complete these stems with words they have seen previously in the encoding list (i.e., the “primes”) than with equally frequent alternatives. This effect is called “priming” (Roediger & McDermott, 1993). Another commonly used priming task is the picture-fragment completion task. In this task, participants encode a series of line drawings. Later they are presented with fragmented pictures and asked to identify them. They are presented with increasingly complete pictures until the picture is identified. Priming is said to occur when participants are quicker to recognize the fragmented pictures that they have seen earlier than novel pictures (Roediger & McDermott, 1993; Sellal et al., 1992).

Early studies indicated that BZs such as diazepam (Fang et al., 1987) and oxazepam (Curran & Gorenstein, 1993) did not impair implicit memory relative to placebo participants on the word-stem completion task. However, further research

indicated that a clinical dose of one BZ -- lorazepam -- impaired priming on both word-stem completion and picture fragment completion tasks, relative to the placebo-treated participants (Bishop & Curran, 1995; Bishop et al., 1996; Brown, Brown, & Bowes, 1989; Sellal et al., 1992). In 1993, Curran and Gorenstein directly compared the effects of clinical doses of oxazepam and lorazepam on an implicit memory task. Participants encoded a word list at 120 minutes post-drug and were later asked to complete a word-stem completion task. The results indicated that lorazepam impaired priming, while oxazepam did not.

The finding that lorazepam impairs implicit memory is a very intriguing finding because implicit memory is not affected by most other variables. Possible reasons given for this finding include a different cortical distribution of lorazepam or a different population of BZ receptors uniquely affected by lorazepam (Brown, Brown, & Bowes, 1989; Curran & Gorenstein, 1993). Until recently, it was believed that only lorazepam impaired priming. However, recent research suggests that other BZs including diazepam (Vidailhet et al., 1994), alprazolam (Fleishaker et al., 1995), and oxazepam (Stewart et al., 1996) may also impair implicit memory. Recently, it has been suggested that the variable findings regarding the effects of BZs on implicit memory might be influenced by the absorption rates of the BZs and the time of the memory encoding relative to drug ingestion in the various studies (Legrand et al., 1995). I will focus on this "time-dependence hypothesis" in this thesis.

Summary. Until recently, research indicated that only one BZ – lorazepam – impaired implicit memory. Findings that dispute this claim, and suggest that other BZs impair priming, will be the main focus of this thesis. Priming is an ever-present occurrence in

our lives and underlies our ability to complete many tasks. The impairment of this process would have serious implications for the ability of individuals to adequately function after taking a BZ (Tulving & Schacter, 1990).

Separating the BZ-Induced Amnesic Effects from Sedation and Attentional Impairments

As noted earlier, BZs produce profound increases in subjective sedation, slow psychomotor and cognitive processing speed, and lead to attentional impairments. It is possible that the memory deficits associated with BZ administration are simply by-products of these other cognitive impairments. Obviously, if a participant is too sedated or inattentive to encode a word list, it will appear as though his/her memory is impaired. Sedation and/or inattention may contribute to memory encoding difficulties, rather than these effects proving to be primary BZ-induced memory impairments. Researchers have attempted to dissociate the amnesic effects of BZs from sedation and inattention in several ways. In general, these findings suggest that even when sedation and attentional impairments are controlled, memory impairments remain.

First, most studies indicate that when performance scores on tasks measuring attention or sedation are treated as covariates, the magnitude of the BZ-induced memory effects may be reduced, but the effects still remain significant or marginally significant (Bishop et al., 1996; Curran et al., 1987b; Stewart et al., 1996). These findings suggest that inattention and sedation cannot fully account for BZ-induced memory impairments. However, as noted by Curran et al. (1991) a difficulty with analysis of covariance is that the procedure assumes a linear relationship between variables, which may not always be the case.

Lending further support to these findings, the majority of studies indicate that the use of flumazenil, a BZ-receptor antagonist, reverses the sedative and attentional effects of BZs while leaving the memory impairment effects intact (Curran & Birch, 1991; Hommer, Weingartner, & Breier, 1993). An additional study found a complete reversal of sedative and attentional BZ effects and a partial reversal of BZ-induced amnesic effects (Flumazenil Study Group, 1992). If BZ-induced memory deficits are still wholly or partially apparent when the sedation and attentional impairments are eliminated pharmacologically, it is likely that the amnesic effects of BZs are not entirely determined by these other factors. The reason that a BZ-receptor antagonist fails to block the amnesic effect of BZs is not known. One possibility is that BZ-induced sedative and attentional effects versus amnesic effects are subserved by different populations of BZ receptors, which in turn are differentially blocked by flumazenil. Indeed, different subtypes of BZ receptors have been identified (see Montaldo et al., 1984; Podhorna, in press). However, this explanation appears unlikely given that flumazenil has been shown to show equal affinity for different subtypes of BZ receptors (e.g., Hantraye et al., 1984). An alternative explanation is that different percentages of BZ receptors need to be occupied to produce the various cognitive effects of BZs (Hommer et al., 1993). Perhaps the attentional and sedative effects require higher percentage of receptor occupation, while the amnesic effects occur at lower occupation. Therefore, the concentration of flumazenil used in previous studies might be sufficient to block BZ-induced inattention and sedation, but insufficient to completely block the amnesic effects. This hypothesis would help explain why Curran and Birch (1991) found no reversal of amnesia using .50 mg of flumazenil while the Flumazenil Study Group (1992) found partial reversal using

an average dose of .73 mg. Lending further support to this hypothesis is a recent study that used a relatively high dose of flumazenil (1.0 mg) and found that the explicit amnesic effects of triazolam were completely reversed (Wesenten, Balkin, Davis, & Belenky, 1995). However, the receptor occupancy hypothesis is not consistent with the results of Hommer et al. (1993) who used a much larger dose of flumazenil (.035 mg/kg) than Wesenten et al. (1995) and did not find reversal of amnesia (i.e., the Hommer et al. dose would be about 2.4 mg for a 68 kg participant). Clearly, further research is needed in this area.

The occurrence of sedation without amnesia also lends indirect support to the idea of BZ-induced primary memory deficits. In one study, lorazepam was compared with the anti-psychotic medication, chlorpromazine. The results indicated that the two drugs induced equal levels of sedation, but that only lorazepam impaired memory (Green et al., 1996). In a second study, BZ-treated participants showed similar levels of sedation to individuals suffering from sleep deprivation. However, only the participants who had taken a BZ were impaired on the memory tasks (Fluck et al., 1998). The fact that certain manipulations (i.e., sleep deprivation and chlorpromazine administration) induce levels of sedation equal to that of BZs, but fail to induce memory impairments, provides further support that BZ-induced amnesia is not merely a by-product of sedation.

Finally, studies using repeated dose administrations indicate that tolerance to the various cognitive side-effects associated with BZ use increases differentially. One study indicated that tolerance to the objective and subjective sedative effects of BZs developed within three weeks. However, memory performance remained impaired over this same interval (Ghoneim, Mewaldt, Berie, & Hinrichs, 1981). Another study indicated that

long-term users of BZs were tolerant to the psychomotor effects, but not the amnesic effects of the drug (Gorenstein, Bernik, & Pompeia, 1994). Overall, it appears that tolerance develops to the sedative effects of BZs, but does not occur for all aspects of memory impairment (Curran, 1992; Curran et al., 1994; Lucki et al., 1986). In a study of individuals who had taken BZs regularly for an average of 10 years, the results indicated that attention and objective sedation were not impaired after administration of an acute dose of BZ. However, some aspects of memory performance remained significantly impaired (Curran, 1992).

Overall Effects of BZs on Human Cognition

Overall, studies using a wide variety of BZs, and numerous experimental paradigms, indicate that sedation is increased, and attentional processes are impaired after an acute dose of a BZ. However, these impairments are subject to tolerance, and are not a major problem for long-term BZ users. Memory deficits, however, appear to be severe and long-lasting. BZs impair long-term memory in an anterograde fashion. These memory deficits are not simply by-products of the detrimental effects of BZs on sedation and attention.

Focus of the Present Series of Studies

The body of research contained in this thesis was designed to examine and extend the results of these recent studies that have suggested that BZs might have a time-dependent effect on implicit memory (e.g., Stewart et al., 1996). Study 1 was designed to examine the hypothesis that therapeutic doses of BZs will impair implicit memory if participants encode the to-be-remembered stimuli around the time of the theoretical peak blood concentration of the drug. The time-dependent effects of 2 mg lorazepam, 30 mg

oxazepam, and placebo were examined by comparing the effects of each drug on implicit and explicit memory at 170 minutes post-drug. These two drugs have different absorption rates and the 170 minute time point was close to the theoretical peak blood concentration time for oxazepam and past the peak concentration time for lorazepam. I hypothesized that if BZs have a time-dependent effect on implicit memory, oxazepam should be found to impair priming, in contrast to previous studies that examined oxazepam at earlier time-points (i.e., Curran & Gorenstein, 1993). Based on the abundance of research finding explicit memory impairment at many different testing times post-drug administration, I predicted that explicit memory would be impaired by both lorazepam and oxazepam.

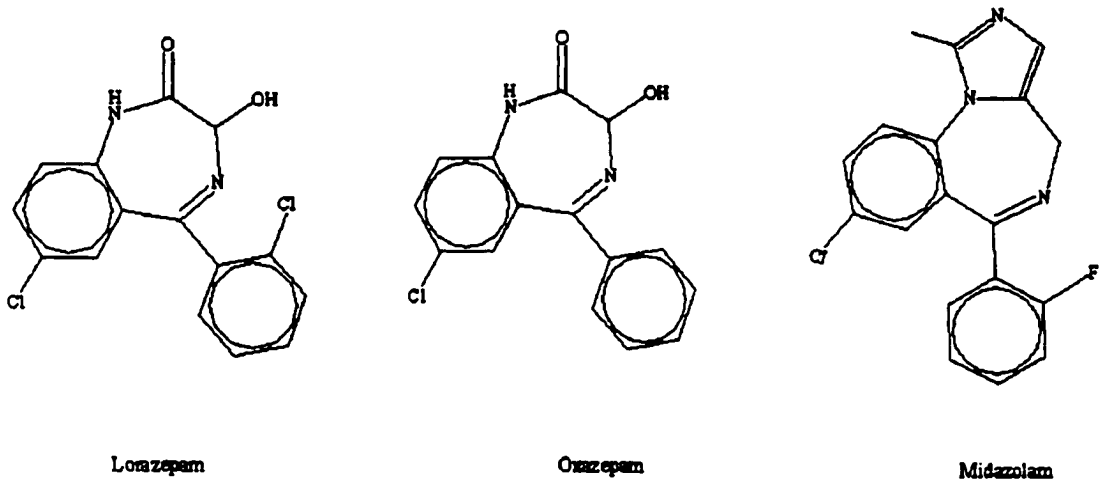
Study 2 was designed to advance the results of Study 1 by further examining the time-dependent memory impairment curve of a single BZ, oxazepam (30 mg). The effects of oxazepam and placebo on an implicit memory task and an explicit memory task were studied at three time points: 100 minutes (pre-peak plasma concentration of 30 mg oxazepam), 170 minutes (close to the theoretical peak plasma concentration of 30 mg oxazepam) and 240 minutes (post-peak plasma concentration of 30 mg oxazepam) after drug administration in a completely between-subjects design. It was hypothesized that oxazepam would impair explicit memory, but not implicit memory, at the pre-peak testing point. In contrast, I predicted that both implicit and explicit memory would be impaired at the peak testing time. Finally, the post-peak testing time was examined in an exploratory fashion, to determine how long-lasting the predicted explicit and implicit memory impairments would be for oxazepam.

Study 3 was designed as an attempt to replicate the time-dependent memory impairment findings of Studies 1 and 2 in an applied setting. Presently, many paediatric hospitals administer a fast-acting BZ, midazolam, to children who are undergoing day surgery, in an attempt to calm and sedate them. Study 3 used a placebo-controlled design to examine the effects of 0.50 mg/kg midazolam at two testing times (pre-peak and peak plasma concentrations of 0.50 mg/kg midazolam), in children who were undergoing myringotomy (ear-tube) surgery. I predicted that implicit memory would only be impaired for subjects who were tested around the time of peak blood concentration of midazolam, lending support to the time-dependence hypothesis in an applied setting. Based on previous studies which found explicit memory impairments due to BZ administration at pre-peak testing times (i.e., Curran & Gorenstein, 1993) and peak testing times (Stewart et al., 1996), I predicted that explicit memory would be impaired by midazolam relative to placebo at both the pre-peak and peak testing times.

In summary, this series of studies was designed to examine the time-dependent effects of BZs on implicit and explicit memory in order to further understand the extent of the cognitive impairments that are associated with BZ use. Throughout this thesis, I use the term “time dependence” because it was time elapsing between drug administration and encoding that was actually manipulated experimentally. However, time was actually manipulated in order to effect differences in blood concentrations of the drug across groups. This was done in order to test the differential effects of various blood concentrations of drug on explicit vs. implicit memory processes. Due to cost/practical issues associated with taking blood samples in the present studies, choice of encoding times in the present research was based on previous findings on relations

between time since drug administration and resultant blood concentrations for particular BZs (e.g., Greenblatt et al., 1981). The chemical structure and key pharmacokinetic and pharmacodynamic features of the particular BZs that are the foci of this thesis are presented in Figure 3.

Figure 3: An Overview of the Chemical Structure, Pharmacokinetics and Pharmacodynamics of Lorazepam, Oxazepam, and Midazolam. Figure is the author's depiction adapted from Sloan and Wala (1998).



Benzodiazepine	Elimination Half-Life ¹	Normal Daily Dose (mg) ²	Absorption Speed ³	Potency ²	Active Metabolite? ^{4,5}
Lorazepam (Ativan™)	Intermediate-Short	1-5	Intermediate-Acting	High	No
Oxazepam (Serax™)	Intermediate-Short	30-90	Slow-Acting	Low	No
Midazolam (Versed™)	Ultra Short	----- ⁶	Fast-Acting	High	No

¹ Greenblatt, Shader, Divoll, & Harmatz, 1981

² Tyrer, 1993

³ APA Task Force, 1991

⁴ Arendt, Greenblatt, Liebisch, Luu, & Paul, 1987

⁵ Higgit, Fonagy, & Lader, 1989

⁶ As midazolam is not used in the long-term treatment of anxiety, typical daily doses of the drug are not available.

CHAPTER THREE: Study 1

An Examination of the Effects of Oxazepam and Lorazepam

on Implicit and Explicit Memory

Research has consistently shown that explicit memory is impaired by a wide variety of BZs (e.g., alprazolam - Allen et al., 1991; lorazepam - Bishop & Curran, 1995). As noted in Chapter 2, early research indicated that only one BZ - lorazepam - impaired both implicit and explicit memory (e.g., Brown et al., 1989; Knopman, 1991).

In 1994, Vidailhet et al. compared the effects of clinical doses of lorazepam and diazepam on picture fragment and word-stem completion tasks. Encoding of the words and pictures took place at approximately two hours post-drug. In contrast to previous studies with diazepam that showed no diazepam-induced priming impairments (Danion et al., 1990; Danion et al., 1989; Fang et al., 1987), both lorazepam and diazepam impaired implicit memory. As noted by the researchers (Vidailhet et al., 1994), the time elapsed between drug administration and encoding was longer in this study than in the previous studies which found no impairment of priming by diazepam (previous encoding occurred at 45-60 min. post-drug). The researchers suggested that diazepam might impair priming if enough time is allowed for the drug to take effect. The theoretical time to peak blood concentration for a clinical dose of diazepam is 61 minutes, so the previous encoding times post-drug may have been too early to observe diazepam-induced priming impairments (Legrand et al., 1995). A study also found impaired priming after alprazolam administration, with encoding occurring at 1 and 3 hours post-drug (Fleishaker et al.,

1995). The theoretical time to peak blood concentration for a clinical dose of alprazolam is 75 minutes post-drug (Fleishaker et al., 1995). This study lends further support to the idea that a number of BZs may impair implicit memory (Fleishaker et al., 1995).

In 1995, Legrand et al. noted that the novel findings of Vidailhet et al. (1994) could be explained by the different absorption rates of BZs. As noted in Chapter 1, BZs are absorbed at different rates, and these speeds are important predictors of their clinical effects (Greenblatt, Shader, Divoll, & Harmatz, 1981). Therefore, encoding may need to take place near the time of peak blood concentration of a BZ for impairment on an implicit memory task to be observed. To test this hypothesis, Legrand et al. (1995) examined the effects of clinical doses of diazepam and lorazepam at three time points (50, 130, and 300 min. post-drug) (Legrand et al., 1995). On a picture fragment completion task of implicit memory, results indicated that diazepam impaired priming at 50 min. post-drug, while lorazepam did not impair priming until 130 minutes post-drug. As noted by the researchers, these impairment times are similar to the time of peak plasma concentration for each drug (61 min for a clinical dose of diazepam; 120 minutes for a clinical dose of lorazepam), lending support to the time dependence hypothesis.

There were several problems with Legrand et al.'s (1995) study that made it difficult to conclusively accept the time dependence hypothesis. First, the results indicated contamination of the implicit memory task from the explicit task due to task repetition. Implicit memory tasks should always be presented before explicit tasks, to ensure that the participant does not become aware of the true purpose of the implicit task and consequently use conscious memory retrieval strategies (i.e., explicit memory strategies) to complete the implicit task. If a BZ-treated participant attempts to use their impaired

explicit memory on an implicit memory test, their performance may be decreased on the implicit task (Schacter, Chiu, & Ochsner, 1993). With multiple testing times, a participant will have had previous experience with the explicit task administered at the first testing time before completing the other implicit tasks, increasing the chances of contamination of the later-administered implicit tasks with explicit memory strategies. For this reason, it has been recommended that implicit memory tasks should not be used as repeated measures (Roediger & McDermott, 1993).

A second problem with Legrand et al.'s (1995) study was that the implicit and explicit tasks did not satisfy the "retrieval intentionality criterion" (Schacter, Bowers, & Booker, 1989). That is, the implicit and explicit tasks should be identical, except for the instructions to the participants, if they are to be directly comparable. If explicit and implicit tasks are not similar, differences in BZ effects across tasks might be explained by other confounding factors. For example, a free recall task of explicit memory may have very different cognitive demands than a word-stem completion task of implicit memory.

Stewart et al. (1996) used tasks which satisfied the "retrieval intentionality criterion" to investigate the potential time-dependent effects of clinical doses of lorazepam (2 mg) and oxazepam (30 mg) on priming. Encoding took place at two time points (100 and 170 minutes post drug). The implicit memory task used was a word-stem completion task. This task was followed by a cued-recall explicit memory task, in which participants were again presented with word stems but were asked to complete them with words that they remembered from the encoding list. The results of this study indicated that at 100 minutes post-drug, similar to the results of Curran and Gorenstein (1993), only lorazepam impaired priming, while both lorazepam and oxazepam impaired explicit memory.

However, at 170 minutes post drug, both drugs impaired implicit and explicit memory. These findings suggest the possibility that Curran and Gorenstein's (1993) memory testing at 120 minutes after drug administration may have been too early to detect any impairments of oxazepam on implicit memory. Again, this study lends support to the time-dependence hypothesis: that is, implicit memory is only impaired if it is tested around the theoretical peak blood concentration of the BZ in question. Lorazepam's peak concentration occurs at 120 minutes (see review by Greenblatt, 1981), while oxazepam is not maximally absorbed until 162 minutes (Curran et al., 1987).

The Stewart et al. (1996) study had several limitations. The purpose of Study 1 was to replicate and extend Stewart et al.'s findings after overcoming the three main limitations of the original study:

(1) Possibility of Implicit Memory Contamination with Explicit Memory Strategies. The simplest explanation for the Stewart et al. (1996) finding is that oxazepam, like other BZs (e.g. diazepam; Legrand et al., 1995) impairs priming only when it has reached its theoretical peak plasma concentration. However, another explanation for the Stewart et al. (1996) findings is explicit memory contamination of the implicit task at the second testing point (170 mins. post-drug). As noted by Schacter et al. (1993), responses on a priming task may be affected if participants realize that their memory is being tested and begin to use explicit remembering to complete the task. Due to the repeated memory testing used in the Stewart et al. (1996) study, where all participants were tested at both 100 and 170 mins. post-drug, it is possible that participants had become aware of the true purpose of the implicit task by the second testing cycle. If this awareness caused the participants to complete the task using explicit memory strategies, the implicit test can be

said to have been contaminated by explicit memory processes, which are well known to be impaired by BZs (Curran et al. 1995).

(2) Lack of Attentional Measure. Another potential limitation of the study by Stewart et al. (1996) is the failure to include a measure of attention. Although the researchers did account for the effects of the drugs on sedation, the possibility remains that the drug-induced memory impairments were secondary to changes in attention (Curran et al., 1987). Since BZs impair attention (e.g., Curran, 1991), it is possible that the BZ-treated participants in the Stewart et al. (1996) study may have had difficulty attending to the word list that they were trying to encode, and that observed BZ-induced “memory” impairments were merely secondary to BZ-induced attentional changes.

(3) Lack of Task Involving “Everyday Memory” Demands. Some researchers have argued that an individual's responses on many laboratory memory tests (e.g., memory for word lists) may not reflect his or her responses in real-life situations (Curran, 1986; Jackson, Louwerens, Cnossen, & deJong, 1993) and, therefore, may lack “ecological validity”. The cued recall task used by Stewart et al. (1996) may not test “everyday memory demands” and, therefore, the observed BZ-induced impairments on this commonly used laboratory measure of explicit memory may not reflect real-world memory deficits. A person who is asked to remember a list of relatively “meaningless” words in a lab may not be sufficiently motivated to remember the list. However, the same individual may be quite motivated to remember what groceries they need to buy. In fact, two studies suggest that when memory tests that more closely simulate real-life situations are used, participants show less BZ-induced memory impairment (Allen et al., 1991; Jackson et al., 1993).

In the present study, I attempted to overcome each of the problems inherent in the Stewart et al. (1996) study as follows:

(1) Possibility of Memory Contamination. In the present study I attempted replication of the Stewart et al. (1996) study after omitting the first memory testing cycle. Therefore, if oxazepam was still found to impair priming at 170 minutes post-drug, explicit memory contamination of the implicit task would be much less likely since prior exposure to the two memory tasks had been eliminated.

(2) Lack of Attentional Measure. In this study I included an established measure of attention (i.e. symbol cancellation task (SYCT); Mesulam, 1985), which could be used as a covariate in analyses of memory performance if the participants who received BZs showed attentional impairments relative to placebo.

(3) Lack of Task Involving “Everyday Memory” Demands. A new memory task was developed and added to the present study in an attempt to assess BZ effects on “everyday memory” abilities. For 160 minutes after drug administration, participants were shown a movie and asked questions about their memory for movie details at successive 15 min. intervals. A task using a story presented in a movie format was used as the memory stimulus in the present study for three reasons. First, a movie may be of more interest to participants than traditional memory task stimuli such as word lists. Secondly, this novel task served as an alternate method of testing episodic memory in addition to the cued recall task that allowed for the assessment of convergence of findings across more than one explicit memory measure. Finally, the movie memory task may involve more everyday memory demands than the cued recall of a word list. Therefore, if participants in the BZ

groups showed deficits on the movie memory task it would provide further evidence that BZs do impair everyday memory abilities.

The methods of the current study were identical to those used by Stewart et al. (1996) with the exception of the addition of the movie memory test and attention task, and the limiting of cued word recall and word stem completion testing to 170 minutes post-drug. I hypothesized that both explicit and implicit memory would be impaired by lorazepam and oxazepam at 170 minutes post-drug. This would lend support to the interpretation that the Stewart et al. (1996) findings were not a result of explicit memory contamination of the implicit task, but in fact reflected time-dependent effects of oxazepam in impairing implicit memory processes. Based on previous research on the relative effects of divided attention on explicit versus implicit memory tasks (Rabinowitz et al., 1982), I hypothesized that participants given a BZ would show attentional impairments and that these impairments would contribute to memory impairments on the explicit tasks but not the priming task. On the movie memory task I hypothesized that both the lorazepam and oxazepam groups would show impairment on the memory questions compared to the placebo group. I further hypothesized that this impairment would begin earlier for the lorazepam group than for the oxazepam group because of the differences in the relative absorption rates of oxazepam and lorazepam (Greenblatt, 1981).

Materials and Methods

Participants. Thirty Dalhousie University students (15 males and 15 females) volunteered to take part in the study. Participants ranged in age from 19 to 36 years ($M=22.3$, $SD = 3.4$ years). All participants met a “normal” weight range requirement of 52 to 73 kg for females and 67 to 89 kg for males. These selected weight ranges are healthy young adult

norms (Jette, Sidney, & Lewis, 1990) and were employed in order to obtain plasma drug concentrations that were relatively constant across participants. All participants were healthy, taking no contraindicated medication, and had no history of exclusionary medical illness. None had a history of alcohol or drug abuse and none were long-term users of BZs. Thus, the definition of healthy volunteers in this study refers to participants with no medical conditions or self-reported use of medications that would contraindicate BZ administration. Participants were instructed to abstain from using alcohol and other CNS drugs for 24 hours before the study and to have no more than one cup of coffee on the morning of the study. Participants were also allowed a light breakfast on the morning of the day of testing (example given to participants was toast and coffee). Participants received four course credit points or \$20 as compensation for participating in the study. All participants provided written informed consent before participation. This study had ethical committee approval.

Experimental Design and Drugs. Participants were randomly assigned to one of three groups, with 10 participants per group. The first group received 2 mg lorazepam (Ativan™ - Wyeth-Ayerst), the second group received 30 mg oxazepam (Serax™ - Wyeth-Ayerst), and the third group received a placebo tablet. Drug tablets were given orally following a double-blind procedure. Participants were tested in the morning.

Tasks and Procedure. Beginning 30 minutes prior to drug administration, participants completed a variety of demographic and cognitive measures to ensure pre-drug equivalence between the three groups. First, participants provided demographic information (age, gender, years of post-secondary education). Participants were also weighed and had their height recorded for use in calculation of body mass index (BMI).

Given the evidence of cross-tolerance between alcohol and BZs (see Stewart, Pihl, & Padjen, 1992) participants were administered the Brief version of the Michigan Alcoholism Screening Test (Brief MAST; [Appendix A]; Pokorny, Miller, & Kaplan, 1972) and a measure of weekly alcohol consumption ([Appendix B]; Stewart, Peterson, & Pihl, 1995). Because of the cross-tolerance between alcohol and BZs, people with a high alcohol tolerance may also be tolerant to BZs (see review in Stewart et al., 1992). Therefore, data from participants scoring greater than 5 on the Brief MAST were excluded from study. This is the best Brief MAST cutoff for detecting people with possible alcohol abuse problems (Jacobson, 1989). Participants were screened for a history of BZ use with an author-compiled questionnaire, and individuals with any reported history of long-term BZ use were excluded from the study. Participants were also administered the Drug Abuse Screening Test (DAST; [Appendix C]; Skinner, 1982), to test for drug problems.

To ensure that groups did not differ in cognitive performance prior to drug administration, participants completed an immediate and delayed test of episodic memory using the Logical Memory Test from the Wechsler Memory Scale-Revised (WMS-R; [Appendix D]; Wechsler, 1987), a letter cancellation task to assess attention (LCT; [Appendix E]; Mesulam, 1985), and the Vocabulary test of the Shipley Institute of Living Scale (SIL; [Appendix F]; Shipley, 1940) to assess baseline verbal knowledge. To ensure that the groups did not differ at pre-drug baseline in their subjective levels of sedation, participants were given five visual analogue scales ([Appendix G] VASs) in which they were asked to rate their current state on five 100 mm lines with the following descriptors: alert-drowsy; excited-calm; clear headed-fuzzy; energetic-lethargic; and quick-slow

(Danion et al., 1989). Scores on the five VASs (number of mm's from the left that the mark was placed) were averaged into a mean sedation score that was used as the dependent measure of subjective sedation. The Finger Tapping test (FTT; [Appendix H]; Frith, 1967) was used to evaluate baseline objective sedation.

Immediately following drug administration, participants were shown a movie (150 minutes in length) which none of them had ever seen before (i.e., *Riel*; Bloomfield, 1979). Every fifteen minutes the movie was paused for one minute and the participants were asked to write down the answers to five brief, orally-administered open-ended questions about what had happened during that section of the movie ([Appendix I]; e.g., "What color was Louis Riel's [the main character] jacket?"). These questions were pilot tested with non-drugged participants to establish a similar difficulty level for all ten sets of questions. The pilot testing was aimed at developing sets of questions that would enable non-drugged participants to achieve an average of 80% correct responses to each of the ten sets of five movie memory questions.

The word lists used for the encoding, explicit and implicit tasks were those used by Stewart et al. (1996) at their first post-drug testing cycle (100 minutes post-drug) ([Appendix J]; Graf & Williams, 1987). In the complete set of 92 words, each word had a unique three-letter word stem. The complete set was divided into four sets of 23 words that were combined to create two encoding sets of 46 words (Stewart et al., 1996). The four lists were balanced for number of letters, frequency of use in the English language (Thorndike & Lorge, 1944), base rate completion of the stem with the target word for a sample of drug-free participants (e.g. Graf & Williams, 1987) and number of possible word stem completions (Carroll et al., 1971) (see Stewart et al., 1996).

After the movie task, participants were again asked to complete the five VASs to measure their post-drug sedation. They were also given an alternate form of the attention task (symbol cancellation task (SYCT; [Appendix K]; Mesulam, 1985). These two tasks were completed beginning at 160 minutes post-drug.

Next, participants completed a semantic encoding task in which they were asked to provide verbal likability ratings to one of the two encoding sets of 46 words. This task took place 170 minutes after drug administration. To maintain consistency with the instructional set used by Stewart et al. (1996) in their second memory testing cycle, the participants were informed that they were going to be asked about the words at a later time (intentional learning instructions). The presentation of the two encoding lists was counter-balanced within each Drug Group. The encoding task was presented on a computer screen with each word remaining on the screen for 5 seconds. Participants were instructed to read each word aloud and rate how much they liked or disliked it on a 5-point scale ([Appendix L]; Brown et al., 1989; Knopman, 1991; Curran & Gorenstein, 1993; Stewart et al., 1996). This rating was given verbally during the inter-stimulus interval (3 seconds). After the participants completed the encoding task they were administered a 90 second objective sedation task (Digit Symbol Test; [Appendix M]; Wechsler, 1981), which also served as a distractor task. Next, participants were provided with a list of 46 word stems and asked to complete them with the first word that came to mind ([Appendix N]; implicit task). The participants were not told anything about the purpose of the word-stem completion task. They were asked to complete the stems in the order they were listed on the form and not to use proper nouns to complete the stems. Participants were given unlimited time on this task but were asked to work as quickly as

they could. There were two forms of the implicit task containing 23 words from the previously shown encoding list (primed) and 23 words from the non-target encoding list (unprimed). Presentation of the two forms of the implicit task was counterbalanced within each Drug Group. Counter-balancing for content of the implicit test across primed/unprimed conditions was achieved through the use of two encoding sets and two forms of the implicit task. For example, for form 1 of the implicit task the same stems that served as “primed” stems for a participant who received encoding set 1, would serve as “unprimed” stems for a participant who received encoding set 2. The inclusion of a balanced set of unprimed stems allowed for an evaluation of potential Drug Group differences in chance generation of target words on the word stem completion task (Greene, 1986).

Following the implicit task, participants were given one of four sets of the 23 stems which began the remaining words from the encoding set which were not used for the implicit task. Participants were given five minutes and instructed to complete the stems with words from the encoding task ([Appendix O]; cued recall). Participants were instructed not to use proper nouns to complete the word stems. Thus, this test was identical to the implicit task except that the instructions to participants differed. Participants were told to guess if they were unsure and were allowed to complete the stems in any order.

Results

Statistical Analysis. Drug Group effects were examined with separate ANOVAs or ANCOVAs with the aid of the Bio-Medical Data Programs (BMDP) statistical software package, Versions P4V and P2V (Dixon et al., 1985). Significant main effects were

followed by Newman-Keuls post hoc comparisons. Correlations between variables were computed with the aid of the BMDP program, Version P6R. Although most dependent variables were examined with separate one-way (Drug Group) ANOVAs, on the implicit memory task, the number of stems completed with targets was analyzed with a 3x2 (Drug Group x Priming Level) ANOVA with repeated measures. Likewise, for subjective sedation, a 3x2 (Drug Group x Time) ANOVA with repeated measures was conducted which compared participant's pre- and post-drug VAS ratings of sedation.

Participant Characteristics. There were no significant effects of Drug Group for any of the control measures. Therefore, the three groups (placebo, oxazepam and lorazepam) did not differ significantly in age, education level, body mass index (BMI) scores, alcohol problems (Brief MAST scores), drug problems (DAST scores), typical weekly alcohol use (drinks per week), and gender composition. Means (and SDs) for these variables (as a function of Drug Group) are illustrated in Table 1.

Table 1
Means (and SDs) on the Control Measures as Functions of Drug Group

<u>Measure</u>	<u>Drug Group</u>		
	<u>Placebo</u> <u>(n=10)</u>	<u>Oxazepam</u> <u>(n=10)</u>	<u>Lorazepam</u> <u>(n=10)</u>
Age - in years	21.60 (2.46)	23.10 (4.86)	22.20 (2.66)
Education Level - yrs. post-secondary education	2.80 (1.92)	4.10 (1.91)	3.80 (1.62)
BMI - weight (kg)/height(m) ²	22.46 (1.70)	22.24 (1.88)	22.56 (2.35)
Alcohol Problems - Brief MAST scores	.00 (.00)	.30 (.67)	.20 (.63)
Drug Problems - DAST scores	1.80 (2.48)	1.00 (1.15)	.40 (.52)
Alcohol Use - Drinks per week	4.78 (4.34)	3.75 (2.56)	3.60 (2.92)
Gender Composition - Percent female	30.00	50.00	70.00

BMI = Body Mass Index; Brief MAST = Brief version of the Michigan Alcoholism Screening Test (Pokorny et al., 1972); DAST=Drug Abuse Screening Test (Skinner, 1982).

Pre-Drug Cognitive Functioning. There were no significant effects of Drug Group on any of the pre-drug cognitive measures. Therefore, the three groups (placebo, oxazepam and lorazepam) did not differ significantly on pre-drug measures of immediate and delayed episodic memory, vocabulary, subjective sedation, objective sedation, and attention (a combined score of time taken to complete the LCT and omission errors on the LCT). No participants had commission errors on the LCT. Means (and SDs) for these variables (as a function of Drug Group) are illustrated in Table 2.

Table 2
Means (and SDs) on the Pre-Drug Measures of Cognitive Functioning, as Functions of Drug Group

<u>Test</u>	<u>Drug Group</u>		
	<u>Placebo</u> <u>(n=10)</u>	<u>Oxazepam</u> <u>(n=10)</u>	<u>Lorazepam</u> <u>(n=10)</u>
Immediate Memory - WMS-R Logical Memory – IM	22.70 (7.38)	24.10 (8.94)	24.90 (3.87)
Delayed Memory - WMS-R Logical Memory – DM	17.10 (8.41)	21.00 (9.92)	20.90 (4.01)
Vocabulary Knowledge -SIL Vocabulary Test Score	30.50 (4.40)	31.70 (7.86)	29.70 (4.57)
Subjective Sedation - Mean VAS rating	52.80 (16.12)	43.12 (11.75)	39.08 (16.55)
Objective Sedation - Mean ITI (msec) on FTT)	256.13 (131.70)	206.30 (35.76)	207.94 (23.32)
Attention Score - Combined score on LCT	85.82 (17.00)	77.64 (21.82)	83.00 (23.94)

WMS-R = Wechsler Memory Scale - Revised (Wechsler, 1987); SIL = Shipley Institute of Living Scale (Shipley, 1940); Subjective Sedation = Mean of five 0-100 visual analogue scales (VASs) of subjective sedation (Danion et al., 1989); Objective Sedation = Mean inter-tap interval (ITI) in msec, on Finger Tapping Test (FTT; Frith, 1967), Combined score on LCT = Time Taken on LCT (sec) + (number of omission errors on LCT * 1.43 [1.43 = mean sec. taken to mark one target on LCT]).

Memory Effects

Movie Memory Task. To ensure that the participants' responses on the movie task were objectively scored by the researcher who had tested the participants, a second individual, who had no contact with the participants also scored each answer. The inter-rater reliability coefficient was very high ($r = .987$). To minimize the number of statistical comparisons on the movie memory task data, the 9 sets of movie questions (5 questions per set) were combined into 3 time blocks. Block 1 contained the 15 questions that asked about memory for movie details from 16 minutes to 63 minutes post-drug administration. Block 2 contained the 15 questions administered from 64 minutes to 111 minutes post-drug. The final Block contained the remaining 15 questions from 112 minutes post-drug to the completion of the movie (160 minutes post-drug). The five questions that asked about memory for the details of the first 15 minutes of the movie were considered a practice phase to familiarize participants with the task, prior to expected onset of drug-induced episodic memory impairments. By examining the number of movie questions that each Drug Group correctly answered at each time block (Figure 4), a distinct pattern can be observed. It appears that the placebo group showed relatively constant performance across the trial blocks. In contrast, the lorazepam group shows rapid deterioration of performance across time blocks, with the performance of the oxazepam group falling midway between that of the other two groups by the third time block.

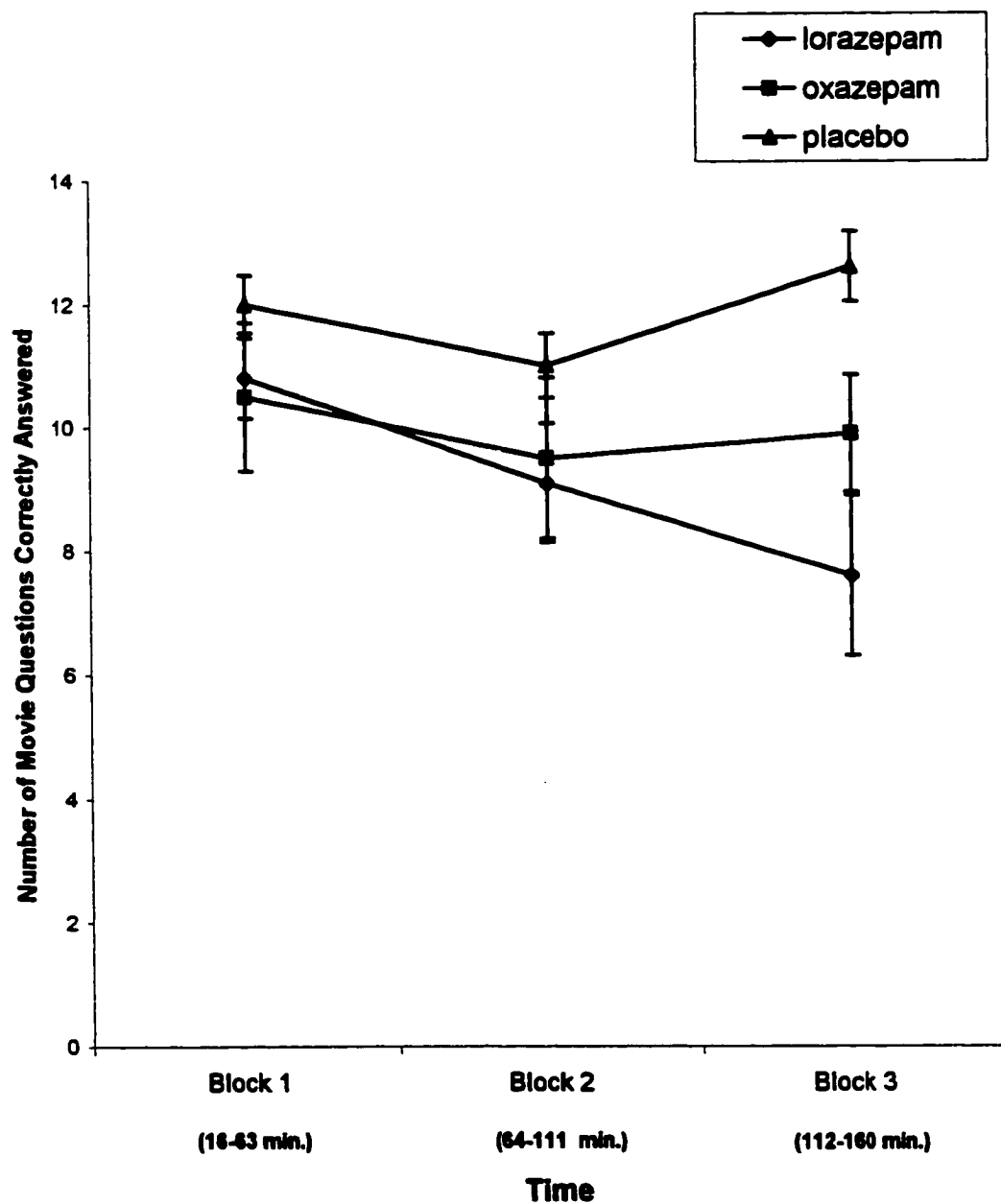
Movie memory performance was analyzed using a 3 x 3 (Drug Group x Time Block) ANOVA with repeated measures. The results indicated a marginally significant effect of Drug Group ($F(2,27) = 2.88, p = .073$) and a significant main effect of Time Block ($F(2, 27) = 4.52, p < .05$). In addition, the interaction between Time Block and Drug

Group was significant ($F(2,27) = 3.58, p < .05$). To further explore the interaction, I examined the simple main effects of Drug Group at each Time Block. The simple main effect of Drug Group was not significant at Time Block 1 ($F(2,27) = 0.93, n.s.$) or at Time Block 2 ($F(2,27) = 1.03, n.s.$). However, the simple main effect of Drug Group was significant at Time Block 3 ($F(2,27) = 6.61, p < .005$).

Given a priori predictions, the movie memory data were also examined using planned comparisons (Tabachnick & Fidell, 1989). First, we hypothesized that the lorazepam group would show impaired memory compared to the placebo group by Time Block 2 of the movie memory test and that this impairment would also be evident at Time Block 3. These hypotheses were evaluated by comparing the placebo and lorazepam group at each of the three Time Blocks. At Time Block 1 there was no significant difference between the two groups ($F(1,18) = 2.25, n.s.$). At Time Block 2 there was a marginally significant difference between the two groups with the lorazepam group showing poorer performance ($F(1,18) = 3.01, p < .10$). At Time Block 3, the lorazepam group was significantly impaired relative to the placebo group ($F(1,18) = 12.73, p < .01$). We also predicted that the oxazepam group would show impaired memory compared to the placebo group, but that this impairment would not be evident until Time Block 3. To evaluate this hypothesis the performance of the placebo and oxazepam participants on the movie memory questions were compared at each Time Block. At Time Block 1 and Time Block 2 there were no significant differences between the two groups ($F(1,18) = 1.40, n.s.$; $F(1,18) = 1.12, n.s.$, respectively). However, at Time Block 3, the oxazepam group was impaired relative to the placebo group ($F(1,18) = 6.11, p < .05$). Overall, these results supported our hypotheses that both Drug Groups would show impaired memory

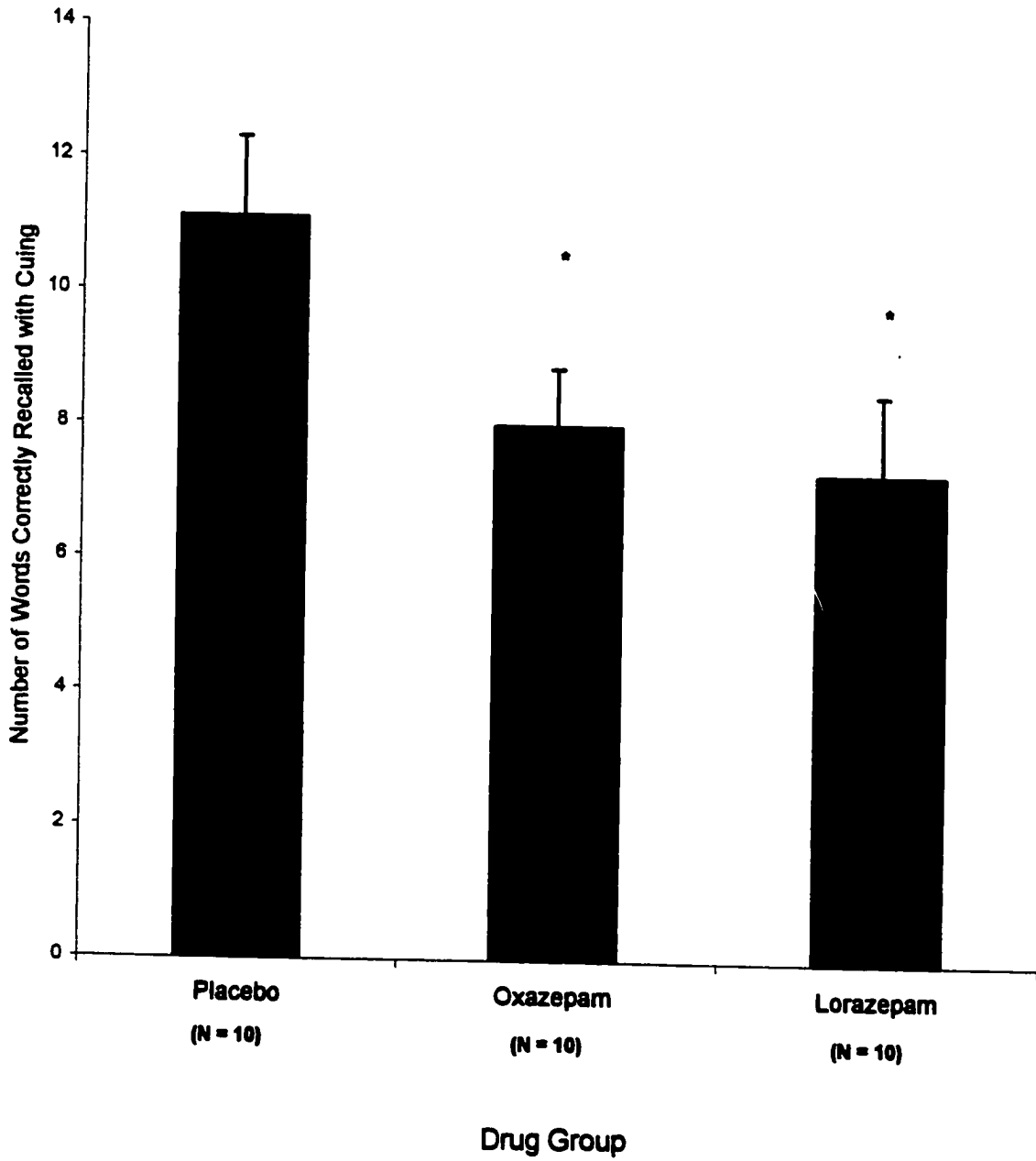
performance when compared to the placebo group, and that the lorazepam group would show impaired memory performance at an earlier time point than the oxazepam group due to lorazepam's faster rate of absorption (Greenblatt, 1981).

Figure 4: Number of Movie Questions Correctly Answered at Three Post-Drug Time Blocks as a Function of Drug Group. Bars represent standard errors.



Explicit Memory. Cued recall performance was scored as the total number of word stems correctly completed with target words from the semantic encoding task. Means (and standard errors) for the cued recall task, as a function of Drug Group, are displayed in Figure 5. The analysis revealed a significant main effect of Drug Group ($F(2,27) = 3.51, p < .05$). Further analyses revealed a significant difference between the placebo and lorazepam groups ($Q(3,27) = 4.97, p < .01$) and between the placebo and oxazepam groups ($Q(2,27) = 4.06, p < .01$) with the placebo group correctly completing more word stems in each case. There was no significant difference between the performance of the lorazepam and oxazepam groups ($Q(2, 27) = .92, n.s.$) on this task (see Figure 5).

Figure 5: Explicit Memory Performance: Mean Number of Words Correctly Recalled on the Cued Recall Test, as a Function of Drug Group. Bars represent standard errors.



Implicit Memory. Analysis of the total number of word stems completed with any word by each Drug Group was not significant ($F(2, 27) = .17, n.s.$). No participant completed less than 41 of the 46 word stems. The implicit memory test was scored as the number of primed word stems and unprimed word stems that were completed with target words from the encoding lists. Means (and standard errors) for the number of stems completed with targets (as a function of Drug Group and Priming Level) are shown in Figure 6. Results indicate a main effect of Drug Group ($F(2, 27) = 4.51, p < .05$), a main effect of Priming Level ($F(1, 27) = 59.94, p < .0001$) and a Drug group x Priming Level interaction ($F(2, 27) = 4.07, p < .05$). The main effect of Priming Level was due to a greater number of primed word stems being completed with targets compared to unprimed stems. The main effect of Drug Group was due to the placebo group completing more word stems with targets than the active Drug Groups. To further investigate the interaction, simple effects of Drug Group were examined at each level of Priming. For the unprimed word stems, there was no simple main effect of Drug Group ($F(2, 27) = .97, n.s.$). Therefore, drug administration did not affect participant's chance performance in generating unprimed targets. However, for the primed stems there was a significant simple main effect of Drug Group ($F(2, 27) = 5.44, p < .05$). Further analysis indicated that the placebo group generated significantly more primed targets than both the lorazepam ($Q(3, 27) = 6.51, p < .01$) and oxazepam groups ($Q(2, 27) = 4.16, p < .01$). The performance of the oxazepam and lorazepam groups did not differ significantly ($Q(2, 27) = 2.35, n.s.$). An index of the amount of priming was calculated for each Drug Group by dividing the group's overall performance on the primed stems by its performance on the unprimed stems. In comparing these indices, it can be seen that completion of primed stems with

targets was about three-and-a-quarter times chance levels for placebo, but only two to two-and-a-half times chance for the lorazepam and oxazepam groups (see Figure 7). It should be noted that no statistical comparisons were performed on these priming index scores. They are displayed in Figure 7 as a function of Drug Group for illustrative purposes only.

Figure 6: Implicit Memory Performance: Mean Number of Stems Completed with Target on the Word-Stem Completion Test, as a Function of Drug Group and Priming. Bars represent standard errors.

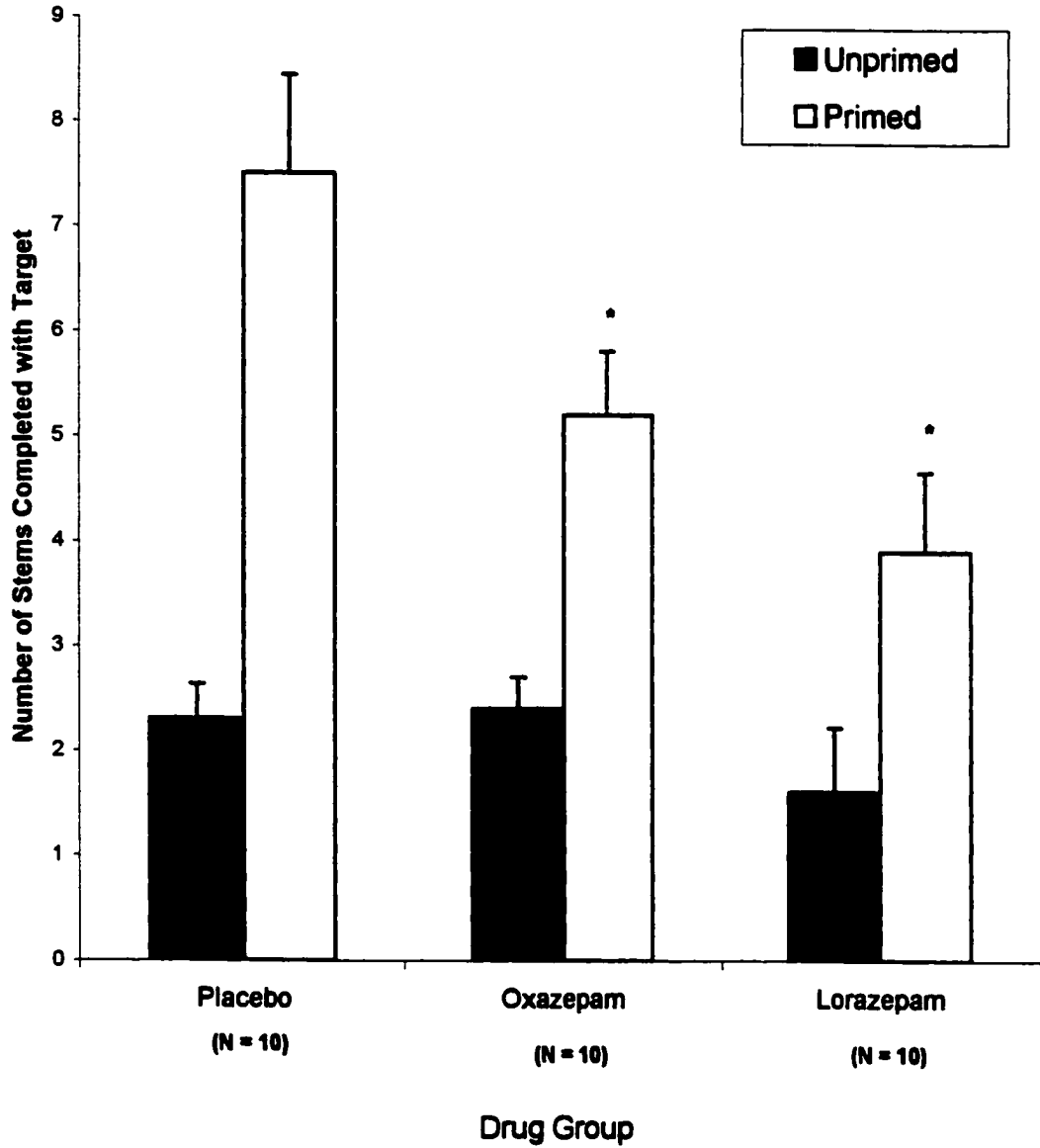
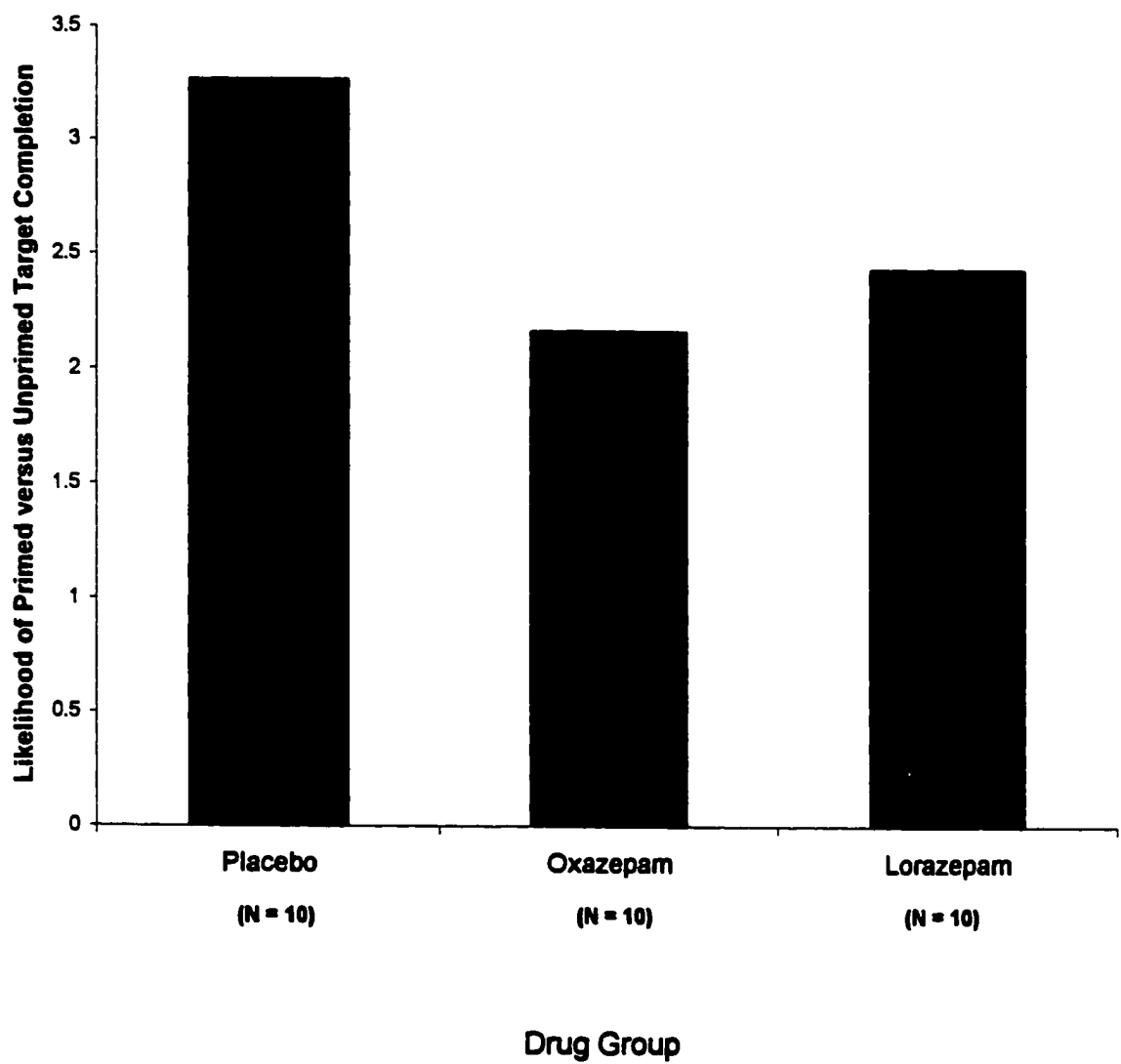


Figure 7: Amount of priming (above chance levels), as a function of Drug Group.



Subjective Sedation. Results indicated no significant main effect of Drug Group ($F(2, 27) = .57$, n.s.). However, there was a significant main effect of Time ($F(2,27)=23.31$, $p<.0001$) and a significant Drug Group \times Time interaction ($F(2, 27) = 9.34$, $p<.001$). To further explore this interaction an analysis of simple effects of Drug Group was performed at each Time. There was no significant simple main effect of Drug Group before drug administration ($F(2,27) = 2.22$, n.s.). However, after drug administration there was a significant main effect of Drug Group ($F(2,27)=6.49$, $p<.01$). Mean (and SD) post-drug subjective sedation ratings are illustrated in Table 3a as a function of Drug Group. Further analysis indicated that the placebo group was less sedated after drug administration than the lorazepam group ($Q(3, 27) = 7.06$, $p<.01$) and the oxazepam group ($Q(2, 27) = 4.78$, $p<.01$) (see Table 3a). The oxazepam group and lorazepam group were not significantly different from each other ($Q(2, 27) = 2.28$, n.s.) (see Table 3a). Simple effects of Time were also performed for each Drug Group. There was a significant simple main effect of Time for the lorazepam ($F(1, 27) = 29.16$, $p<.0001$) and oxazepam ($F(1,27) = 12.49$, $p<.01$) groups, with greater subjective sedation ratings post-drug compared to pre-drug. However, there was no effect of Time for the placebo group ($F(1,27) = .33$, n.s.).

Objective Sedation. Means (and SDs) for the Digit Symbol task are shown in Table 3b, as a function of Drug Group. The number of items correctly completed in 90 seconds on this psychomotor speed task by the three groups showed a similar pattern to those obtained by Stewart et al. (1996), with the BZ participants appearing to be somewhat impaired compared to the placebo participants (see Table 3b). However the Drug Group main effect did not prove statistically significant, ($F(2, 27) = 1.77$, n.s.).

Attention Task. Mean number of omissions on the symbol cancellation test (SYCT) (Mesulam, 1985) and time taken to complete the SYCT were combined to create a combined attention score on the SYCT (time (sec) + number of omission errors * 1.03 [average time in sec. for placebo participants to mark one target]). This combined score was used as a post-drug measure of attention (Curran et al., 1987). Commission errors were not scored because all participants failed to make any such errors on this task. Means (and SDs) for the combined attentional measure are shown in Table 3c as a function of Drug Group. Analysis of this combined score revealed a trend for a Drug Group effect, ($F(2, 27) = 2.88, p = .07$) (see Table 3c). As Bishop and Curran (1995) have reported significant lorazepam-induced impairments on the same attention task, post-hoc comparisons were performed. The lorazepam group had impaired performance on the SYCT, as compared to the placebo group ($Q(3, 27) = 4.50, p < .05$) group (see Table 3c). The performance of the oxazepam group fell midway between that of the lorazepam and placebo groups (see Table 3c). However, the oxazepam group did not differ significantly from either the placebo ($Q(2, 27) = 2.64, n.s.$) or lorazepam ($Q(2, 27) = 1.85, n.s.$) groups (see Table 3c).

Table 3a, b, c
Means (and SDs) on the Post-Drug Measures of Sedation and Attention (a. Subjective Sedation, b. Objective Sedation c. Attention) as Functions of Drug Group

Measure	Drug Group		
	Placebo (n=10)	Oxazepam (n=10)	Lorazepam (n=10)
a. Subjective Sedation			
Mean VAS rating	49.14 ^{ab} (4.74)	65.74 ^b (5.14)	73.64 ^a (4.84)
b. Objective Sedation			
Mean Symbol Digit Test score	62.10 (9.35)	57.80 (9.29)	54.60 (8.17)
c. Attentional Measure			
Mean Combined Score on the SYCT	62.84 ^c (11.11)	73.01 (14.38)	80.76 ^c (24.39)

Subjective Sedation = Mean of five 0-100 visual analogue scales (VASs) of subjective sedation (Danion et al., 1989); Objective Sedation Task = Post- Drug Digit Symbol Test (Wechsler, 1981) score. Attention = Time (sec.) taken on SYCT + (number of omission errors * 1.03 [mean time in sec. taken by placebo participants to mark one target]). (SYCT; Mesulam, 1985). All comparisons are across Drug Groups. Means with similar superscripts are significantly different from one another: ^ap<0.01, ^bp<0.01, ^cp<0.05.

Covariation Between Cognitive Impairments and Performance on the Memory Tasks. A series of Analyses of Covariance (ANCOVAs) were conducted which covaried out post-drug subjective sedation, pre-post subjective sedation change scores and combined attention scores, respectively, from the scores on the implicit task (word-stem completion), explicit task (cued-recall), and the last time block of the movie memory task. Objective sedation was not covaried because there were no significant effects of Drug Group with this task. For attention, only post-drug scores could be covaried because this task was only administered once (i.e., slightly different attentional tasks were administered before vs. after drug administration). In contrast, the same subjective sedation measure was administered after drug administration as was administered prior to drug administration. Thus, I used both post-drug subjective sedation and pre-post change in subjective sedation as covariates to ensure consistency of results across these two methods of analyses.

Covarying subjective sedation change scores, post-drug subjective sedation scores, and attention scores did not affect the pattern of Drug Group differences or the significance levels of the Drug Group differences ($F(2, 27) = 4.32, p < .05$; $F(2, 27) = 4.27, p < .05$; $F(2, 27) = 4.35, p < .05$, respectively) on the implicit memory task. Also, covarying subjective sedation change scores and post-drug subjective sedation scores did not affect the pattern of Drug Group differences or the significance levels of the Drug Group effects ($F(2, 26) = 4.03, p < .05$; $F(2, 26) = 4.13, p < .05$, respectively) on the cued recall task. However, for the cued recall task, treating the combined attention score as a covariate did not change the pattern of Drug Group means, but appeared to reduce the Drug Group effect ($F(2, 26) = 3.22, p = 0.05$). Although covarying post-drug subjective

sedation did not affect the Drug Group differences on the cued recall and word-stem completion tasks, it appeared to influence the Drug Group differences on the last time block of the movie memory task: the lorazepam group was still significantly impaired relative to placebo ($F(1,17) = 6.44, p < .05$) but the difference between the oxazepam and placebo group appeared to be reduced ($F(1,17) = 3.16, p = .09$). Likewise, after covarying subjective sedation change scores the lorazepam group was still significantly impaired relative to the placebo group ($F(1,17) = 6.31, p < .05$) but the difference between the oxazepam and placebo group appeared to be reduced ($F(1,17) = 1.67, n.s.$). Covarying attention scores also appeared to affect the results of the last time block of the movie memory task in a similar fashion. The lorazepam-treated participants continued to evidence significant movie memory impairments relative to placebo ($F(1,17) = 15.59, p < .001$). The magnitude of the difference between the oxazepam group relative to placebo appeared to be somewhat reduced, but the impairment remained significant ($F(1,17) = 5.70, p < .05$).

Relation Between Stem Completion and Cued Recall. A priming index, calculated by subtracting the number of unprimed stems completed with target words from the number of primed target completions, was determined for each participant. Participants' priming index scores were correlated with the number of correctly completed word stems on the explicit task. The resulting correlation coefficient was positive but not significant ($r = .204, n.s.$), indicating that performance on the implicit task was relatively independent of explicit memory task performance.

Discussion

Overall, in conjunction with the results of Stewart et al. (1996), this study lends stronger support to the hypothesis that BZs have a time-dependent effect on implicit memory. The present results also support previous findings of BZ's impairments of explicit memory (e.g. Danion et al., 1990). In addition, this study extends previous findings of BZ-induced memory impairments to another explicit memory measure that may have more interest to participants (i.e., the movie memory task). Finally, this study is an important addition to previous research that indicates that there is a dissociation between the sedative and cognitive effects of BZs (e.g., Hommer et al., 1993).

Even though the three groups were initially equivalent on all pre-drug cognitive measures, both oxazepam and lorazepam impaired priming compared to the placebo group at 170 minutes post-drug. Unlike the study of Stewart et al. (1996) in which there was a potential for explicit contamination of the implicit task due to repeated testing with the same memory tasks, the participants in the present study were only tested with the cued recall and word-stem completion tasks at one time point. Therefore, it appears that the most likely explanation for this finding is that when oxazepam (30 mg) reaches a specific threshold concentration which appears to occur at a time when it is nearing its peak blood concentration (Greenblatt, 1981) it begins to exert impairments on implicit memory processes.

Like Stewart et al. (1996), the present study used intentional task instructions with participants being informed that they were going to be asked about the encoding stimuli at a later time. This is in contrast to incidental encoding instructions, in which participants are not informed of an upcoming memory task. One might argue that the intentional task

instructions could cause contamination of the implicit memory task, by “warning” participants that a memory task would later appear. However, previous research suggests that while the encoding instructions (incidental versus intentional) may significantly influence performance on the explicit memory task, choice of encoding instructions has no effect on priming (Greene, 1986; Schacter et al., 1993).

The present study used memory tasks that satisfied the retrieval intentionality criterion and, therefore, are directly comparable (Schacter et al., 1989). Although a dissociation between explicit versus implicit memory was not observed directly as a function of drug administration in the present study, the fact that there was no significant correlation between participants' performance on the word-stem completion task and cued recall task lends support to the notion of two separate memory systems (Schacter, 1995). If a participant's ability to perform on the implicit task is not related to his or her performance on the directly comparable explicit task, it is probable that the two memory tasks are actually measuring different constructs. However, it should be noted that the small number of participants in the present study might not have provided enough power to detect a significant correlation.

Many researchers have noted that traditional laboratory tests of memory may lack “ecological validity” (i.e., are not representative of real-life memory requirements) (e.g., Curran, 1986). When participants in the present study were administered a task that appears to be more representative of real-life memory requirements (i.e., the novel movie memory task), lorazepam and oxazepam were still found to impair explicit memory performance. Both the oxazepam and lorazepam groups showed impairments relative to placebo in their ability to recall details pertaining to the story line of a movie from 112

minutes to 160 minutes post-drug. Compared to the oxazepam group, the lorazepam treated participants showed a pattern of earlier episodic memory decline, with impairments marginally evident relative to placebo at the 64-111 minutes post-drug testing point.

These relative rates of episodic memory impairments across the two drugs compared to placebo are consistent with their relative absorption speeds (Greenblatt, 1981). However, empirical data on the actual ecological validity of this novel task needs to be gathered, before any definitive conclusions about BZs' effects on real-world memory abilities can be made.

It should be noted, however, that the memory performance of the placebo-treated participants was not stable across the three time points (appeared to increase at Time Block 3), and this shift in performance may have contributed to the movie memory impairments found. However, this improvement in the placebo group might be an effect of learning (i.e., figuring out the types of questions that I tended to ask) leading to improved performance. In contrast, this learning effect did not occur for either of the BZ-treated groups.

It should also be cautioned that the conclusion that lorazepam effects began earlier than oxazepam effects is based upon the results of a priori planned comparisons which increased the number of statistical comparisons, making the possibility of Type I error greater. Nonetheless, the full 3 x 3 ANOVA results did support a significant interaction between Drug Group and Time Block, with significant benzodiazepine impairments being observed by the third block (112-160 minutes post-drug). This strongly supports the notion that benzodiazepine-induced memory impairments become apparent over time, even on a real-world memory task.

In addition to impairing memory, BZs have many other effects on cognitive processes including effects on sedation and attention (Curran, 1986). In the present study the drugged participants reported more sedation than placebo participants. To help rule out the possibility of subjective sedation causing the memory impairments observed in the present study, a series of analyses of covariance were performed. The participants' reported sedation (as analyzed using both change scores and post-drug sedation scores) did not influence Drug Group effects on priming on the implicit memory (word-stem completion) task or the cued recall test. This is consistent with previous research that indicated that the cognitive effects of BZs do not appear to be dependent on their sedative effects (e.g., Hommer et al., 1993). However, subjective sedation appeared to partially contribute to BZ-induced impairments in movie memory performance. It is thus possible that subjective sedation may have a greater effect on explicit memory tasks that simulate "real-life" situations as compared to traditional laboratory tasks.

In the present study, drugged participants were also marginally impaired on a focused attention test, as compared with the placebo participants. Since Stewart and associates (1996) failed to include an attention task, it is possible that their drugged participants were attending less to the word lists at encoding than placebo participants, and that the memory impairments observed were secondary to these attentional impairments. To help rule out this possibility in the present study, a series of analyses of covariance were performed. As with sedation, participant's attentional impairments did not influence the Drug Group effects on priming in the implicit memory (word-stem completion) task. However, attention did appear to contribute to the Drug Group differences in explicit memory performance (i.e., cued recall (cf., Bishop & Curran, 1995),

as well as movie memory, performance). These findings are consistent with the results of previous research which found that level of processing and divided attention manipulations influence explicit memory performance but do not affect priming (Rabinowitz et al., 1982). Overall, the fact that attentional impairments did not contribute to drug-induced impairments of implicit memory but did contribute to disruptions in explicit memory performance lends further support to the idea that implicit and explicit memory processes are dissociable (Roediger & McDermott, 1993).

In the future, the effects of other BZs on implicit memory should be tested close to the time of peak blood concentration for the BZ in question. In addition, dose response curves for the effects of various BZs on memory need to be obtained (i.e., higher doses of lorazepam may impair priming at an earlier time point than the results obtained with 2 mg). To date only diazepam (Legrand et al., 1995), lorazepam (e.g., Curran & Gorenstein, 1993; Bishop et al., 1996), alprazolam (Fleishaker et al., 1995) and oxazepam (Stewart et al., 1996) have been shown to impair priming; the results of each of these latter studies are consistent with the time-dependence hypothesis. In future studies, other BZs should also be tested at various time points to gain a better understanding of the impairment curves for both implicit and explicit memory. It is recommended that such future studies be conducted as between-subjects designs to reduce the possibility of repeated testing contaminating the implicit task (Roediger & McDermott, 1993).

Based on previous research (Stewart et al., 1996) it appears that oxazepam-induced explicit memory impairments become apparent before impairments of implicit memory. Specifically, it appears that oxazepam impairs explicit memory, but not implicit memory, if memory is tested well before the time of peak blood concentration. In

contrast, near the time of peak plasma concentrations of oxazepam, this drug impairs both explicit and implicit memory. Future research will need to examine the effects of oxazepam on implicit and explicit memory following the time of its peak blood concentration to determine the persistence of both implicit and explicit memory impairments. Also, as dose-dependent effects of BZs on explicit memory have been reported (see Weingartner et al., 1995), future research should examine different doses of oxazepam and lorazepam to determine how dosage is related to the impairment of implicit memory and the time to peak blood concentration for each BZ.

It should be noted that explicit and implicit memory have been tested in lorazepam-treated participants both slightly before, near, and well after, the theoretical peak plasma concentration of lorazepam of approximately 120 minutes post-drug. Thus far, no dissipation of lorazepam-induced explicit memory or implicit memory impairments relative to placebo have been noted (i.e., Stewart et al. (1996) 100 and 170 minutes post-drug; Curran and Gorenstein (1993) 120 minutes post-drug; present study 170 minutes post-drug). Lorazepam has thus been shown to produce impairments on both explicit and implicit memory tasks relative to placebo from 100-170 minutes post-drug. Although these findings do not directly support the time-dependence interpretation, it is possible that the memory testing time may have to be extended more than 50 minutes post-peak, and reduced to more than 20 minutes pre-peak, to observe the hypothesized dissociation between implicit and explicit memory impairments. In fact, Greenblatt and associates (1981) have stated that the duration of action of an acute dose of lorazepam tends to be extended because the distribution of lorazepam is less extensive than the distribution of

other BZs. Therefore, high concentrations of lorazepam can stay in the plasma for many hours.

Overall, it appears that lorazepam and oxazepam cause impairments of both explicit and implicit memory if they are tested near the time of peak blood concentrations for the specific drug in question. BZ-induced explicit memory impairments are apparent even when the memory task administered appears to more closely simulate real-life memory requirements. These demonstrated impairments of both implicit and explicit memory by BZs may make it difficult to effectively use concurrent cognitive or behavioral therapy in the treatment of individuals with anxiety disorders who also take BZs (Curran, 1991; Wardle, 1990). Although chronic BZ users become tolerant to the sedative and attentional effects of BZs, they continue to suffer from memory impairments and it is likely that these difficulties have severe implications for their everyday functioning (Curran, 1992).

CHAPTER FOUR: Study 2

An Examination of Differences in the Time-Course of Oxazepam's Effects on Implicit Versus Explicit Memory

The results of Study 1 suggested that having memory encoding occur close to theoretical peak blood concentrations may be necessary to detect BZ effects on implicit memory. Study 2 was designed to expand upon these findings by investigating the effects of one BZ, with the encoding of memory stimuli occurring at three different times. This methodology will help define the specific time course of the effects of BZs on both implicit and explicit memory.

Recent findings suggest that BZ-induced implicit and explicit impairment curves may actually differ. For example, Stewart et al. (1996) examined implicit and explicit memory at two time points. In the study, memory stimuli were encoded at 100 and 170 min. after administration of oxazepam. The results indicated that at 100 minutes, or before the theoretical peak blood concentration of oxazepam (30 mg), only explicit memory was impaired. However, when tested at 170 minutes, participants showed impairments in both implicit and explicit memory. These results suggest that explicit memory processes may be impaired by oxazepam at an earlier time-point than implicit memory processes (Stewart et al., 1996).

Fleishaker et al. (1995) administered single doses of alprazolam to participants and tested implicit and explicit memory (encoding of memory stimuli took place immediately before each task was administered) at three different time points (60, 180, 360 minutes

post-drug). Plasma concentrations of the drug were also measured with the peak plasma concentration occurring at 75 minutes post-drug. The results indicated that explicit memory, as measured by a free recall task, was impaired by a high dose (1.5 mg) of alprazolam at each of the three testing times. However, implicit memory, as assessed by a fragmented picture task, was only impaired at the 60 and 180 minute testing times by the same dose of alprazolam. This finding suggests that alprazolam-induced explicit memory impairments may persist for a longer time following drug administration than implicit impairments. Little research to date has directly investigated such differences in the time course of BZ-induced impairments in explicit versus implicit memory, however.

Unfortunately, as discussed in Chapter 3 (Study 1), many of the studies which have produced data consistent with the time-dependence hypothesis had a high potential for explicit memory contamination of the implicit memory task, due to the fact that participants were tested at multiple testing periods in a within-groups design (e.g., Curran & Gorenstein, 1993; Legrand et al., 1995; Fleishaker et al., 1996; Stewart et al., 1996). Moreover, some BZ studies which have produced findings suggesting differing implicit and explicit memory impairment curves over time (Fleishaker et al., 1996), used memory tasks which did not satisfy Schacter et al.'s (1989) retrieval intentionality criterion (i.e., the explicit and implicit tasks differed in more than just instructions to participants at time of recollection) and thus should not be directly compared (Roediger & McDermott, 1993). Another possible limitation of most previous studies of BZ effects on memory (e.g., Curran & Gorenstein, 1993; Legrand et al., 1995; Stewart et al., 1996) is that researchers often fail to include a measure of attention. As has been noted previously, it is possible

that any drug-induced memory impairments in these studies are secondary to changes in attention (Curran et al., 1987).

The present study attempted to determine the time course of oxazepam's effects on explicit and implicit memory, in a placebo-controlled design, with memory stimuli being encoded at one of three times: before the peak blood concentration of oxazepam (100 min. post drug administration), close to the theoretical peak blood concentration (170 min. post drug, which is close to oxazepam's (30 mg) peak concentration at 162 mins.; Curran et al., 1987), and after peak blood concentration (240 min. post drug). An independent-groups design was used where separate groups of participants were tested at each encoding time, to reduce the likelihood of explicit contamination of the implicit memory test due to repeated memory testing (Legrand et al., 1995). The present study used an explicit memory test (cued recall task) and an implicit test (word stem completion test), which satisfied Schacter et al.'s (1989) retrieval intentionality criterion. The present study also included measures of sedation and attention in order to ensure that any observed memory effects were not merely secondary to drug-induced changes in sedation or attention during encoding.

Based on previous research with oxazepam (Curran & Gorenstein, 1993), it was predicted that at the pre-peak testing time (100 min. post-drug), oxazepam would impair explicit memory while sparing priming. Also based on previous research with oxazepam (Stewart et al., 1996), it was predicted that at the peak testing time (170 min. post-drug), oxazepam would impair both implicit and explicit memory, relative to placebo, thus supporting the time-dependence hypothesis (Legrand et al., 1995). Finally, based on the findings of Fleishaker et al. (1995) with alprazolam, it was predicted that oxazepam's

effects on implicit memory would be found only at a relatively narrow time window centering around the time of oxazepam's theoretical peak blood concentration. More specifically, it was predicted that only explicit memory but not implicit memory would still be impaired at post-peak (240 min. post-drug).

Materials and Methods

In general, the methods used were identical to those used in Study 1.

Participants. Sixty healthy university students (30 males and 30 females) volunteered to take part in the study. Participants ranged in age from 18 to 36 years ($M=21.70$, $SD = 3.66$). All participants met a "normal" weight range requirement of 52 to 73 kg for females and 67 to 89 kg for males. These selected weight ranges are healthy young adult norms (Jette, Sidney, & Lewis, 1990) and were employed in order to obtain plasma drug concentrations that were relatively constant across participants. All participants were healthy, taking no contraindicated medication, and had no history of exclusionary medical illness. None had a history of alcohol or drug abuse and none were long-term users of BZs. Thus, the definition of healthy volunteers in this study refers to participants with no medical conditions or self-reported use of medications that would contraindicate BZ administration. Participants were instructed to abstain from using alcohol and other CNS drugs for 24 hours before the study and to have no more than one cup of coffee on the morning of the study. Participants were also allowed a light breakfast on the morning of the day of testing. Participants received four course credit points or \$20 as compensation for participating in the study. All participants provided written informed consent before participation. This study had ethical committee approval.

Experimental Design and Drugs. Participants were randomly assigned to either the drug condition or the placebo condition in a double-blind fashion. The participants in the drug condition received 30mg of oxazepam (Serax – Wyeth-Ayerst), administered orally. This dose is within the ‘therapeutic dose range’ typically used for the treatment of anxiety disorders (Curran, 1986). The participants in the placebo condition received a placebo tablet that was identical in appearance to the oxazepam tablet. Within each of these conditions, participants were assigned to one of three testing times: 100 minutes post drug administration, 170 minutes post drug administration or 240 minutes post drug administration. Assignment to encoding time conditions was pseudo-random in that the three conditions were run sequentially: participants in the 100 min. post-drug (“pre-peak”) encoding time were run first (Stewart et al., 1996); participants in the 170 min. post-drug (“peak”) encoding time were run second (Study 1); and participants in the 240 min. post-drug (“post-peak”) encoding time were run third. This pseudo-random assignment did not compromise the double-blind procedure because it is impossible to keep experimenter or participant blind to the time of testing. Identical participant selection criteria and experimental conditions (except encoding instructions) were used at each Encoding Time. Testing sessions began at 8am.

Participants completed a number of demographic and cognitive measures that began 30 minutes prior to drug administration. These measures were used to ensure pre-drug equivalence between the groups. Participants provided demographic information (age, gender, years of post-secondary education) and their height and weight were recorded for use in the body mass index (BMI) calculation. Participants were administered the Brief Version of the Michigan Alcohol Screening Test (Brief MAST

[Appendix A]; Pokorny et al., 1972) and a questionnaire about weekly alcohol consumption ([Appendix B]; Stewart et al., 1995). Because of the cross tolerance between alcohol and BZs, people with a high alcohol tolerance may also be tolerant to BZs (Stewart et al., 1992). Therefore, data from participants scoring greater than 5 on the Brief MAST were excluded from study. One participant was excluded on the basis of this criterion. This is the best Brief MAST cutoff for detecting people with possible alcohol abuse problems (Jacobson, 1989). Participants were screened for a history of BZ use (Stewart et al., 1996), and individuals with any reported history of BZ use were excluded from the study. Participants were also administered the Drug Abuse Screening Test (DAST [Appendix C]; Skinner, 1982), to test for drug problems.

To assess pre-drug cognitive performance, several tests were used. The first baseline cognitive measures were an immediate and delayed test of episodic memory using the Logical Memory Test from the Wechsler Memory Scale - Revised (WMS-R [Appendix D]; Wechsler, 1987). The Vocabulary Test of the Shipley Institute of Living Scale (SIL; [Appendix F]; Shipley, 1940) was used to assess baseline verbal knowledge. To assess pre-drug levels of sedation, participants were given five visual analogue scales ([Appendix G]; VASs). They were asked to rate their current state on five 100 mm lines with the following descriptors: alert-drowsy, excited-calm, clear headed-fuzzy, energetic - lethargic, and quick-slow (Danion et al., 1989). Scores on the five VASs were averaged to create a mean subjective sedation score. The Finger Tapping Test (FTT; [Appendix H]; Frith, 1967) was used as a baseline measure of objective sedation.

After the pre-drug tests were completed, the tablet (oxazepam or placebo pill) was administered. In order to have participants remain alert they were shown one of several

possible movies during the interim between drug administration and cognitive testing; the experimenter remained with participants to ensure that they did not fall asleep. At ten minutes before cognitive testing commenced, participants were again given the VASs to assess the effects of oxazepam on sedation.

The encoding stimuli for the implicit and explicit memory tasks used in the present study were taken from a previous study by Graf and Williams ([Appendix J]; 1987). In the complete set of 92 words, each word had a different three-letter word stem. This set was divided into four sets of 23. These lists were balanced for frequency of use in the English language (Thorndike & Lorge, 1944), number of letters, base rate completion of the stem with the target word for a sample of drug-free participants (e.g. Graf & Williams, 1987), and the number of possible word stem completions (Carroll et al., 1971). The four sets were combined to create two encoding sets of 46 words (Stewart et al., 1996).

At the appropriate testing point, 100 minutes, 170 minutes, or 240 minutes post-drug administration, participants were given the semantic encoding task. Although all participants encoded words semantically, the encoding instructions varied across testing Encoding Times as the participants in the pre-peak and peak testing groups were obtained from two previous studies (see Stewart et al., 1996; and Study 1, respectively): At the pre-peak testing time participants were given incidental learning instructions in which they were not given any information about the upcoming memory tasks (Stewart et al., 1996). At the peak (Study 1) and post-peak testing times, participants were told that they would be asked about these words at a later time (intentional learning instructions). These differences in instructional set at encoding precluded direct statistical comparison of performance at each Encoding Time. The presentation of the two encoding lists was

counterbalanced within each of the six groups. Each word was presented for five seconds on a computer screen. Participants were instructed to read each word aloud and to rate how much they liked or disliked the word on a 5-point scale ([Appendix L]; Curran & Gorenstein, 1993). This likability rating was given orally during the inter-stimulus interval (3 seconds).

After this encoding task, participants were given the post-drug objective sedation measure ([Appendix M] Digit-Symbol Task; Wechsler, 1981), which also served as a distractor before memory testing. Following this distractor, the implicit task was administered. Participants were given one of two possible lists of 46 three-letter word stems and were instructed to complete the stems with the first word that came to mind (Appendix N). They were also instructed to complete the stems in the order presented on the form and to refrain from using proper nouns. Participants were allowed unlimited time to complete this task, but were instructed to work as quickly as possible. This implicit task contained stems corresponding to 23 words from the previously shown encoding list (primed) and to 23 words from the non-target encoding task (unprimed). The inclusion of a balanced set of unprimed stems allowed for an evaluation of potential Drug Group differences in chance generation of target words on the word stem completion task (Greene, 1986). The order of presentation of these two implicit word stem sets was counterbalanced across participants within each Drug Group and Encoding Time.

Following the implicit (word stem completion) task, but prior to the explicit (cued recall) task, the participants were given a test of attention/span memory (Digit-Span Task; [Appendix P] Wechsler, 1981; Lezak, 1995). On this task, comparison of performance on the Digit Span Forward and Digit Span Backward subtests can be used as a measure of

attention: if participants perform well on the Forward test, but poorly on the Backward test, it is attention rather than span memory that is impaired (Lezak, 1995). Finally, participants were presented with one of two forms of the explicit memory test (Appendix O). Each form consisted of 23 three-letter word stems that corresponded to the words in the encoding task that had not been used in the implicit test. Participants were instructed to complete the stems with the words from the encoding task (i.e. cued recall). Therefore, this test was identical to the implicit test with the exception of the instructions given to the participants.

Results

Statistical Analysis. Drug Group effects were examined with separate ANOVAs or ANCOVAs with the aid of the Bio-Medical Data Programs (BMDP) statistical software package, Versions P4V and P2V (Dixon et al., 1985). Correlations between variables were computed with the aid of the BMDP program, Version P6R. Most dependent variables were examined with 2 x 3 (Drug Group x Encoding Time) ANOVAs. However, because different encoding instructions were used at each of the three Encoding Times (see description of the encoding instructions in the experimental design and drugs section), separate one-way (Drug Group) ANOVAs were conducted on the cued memory scores at each Encoding Time. Likewise, implicit memory scores were analyzed separately at each Encoding Time using a 2 x 2 (Drug Group x Priming Level) ANOVA with repeated measures. For subjective sedation, a 2 x 3 x 2 (Drug Group x Encoding Time x Drug Phase) ANOVA with repeated measures was conducted which compared participant's pre- and post-drug VAS ratings of sedation.

Participant Characteristics. A series of 2 x 3 ANOVAs (Drug Group x Encoding Time) were conducted to determine if the groups differed on any of the control variables. The six groups were equivalent in body mass index (BMI), drug and alcohol problems, number of drinks per week, and gender composition. Although 2x3 ANOVAs indicated significant effects of Encoding Time on age ($F(2, 54) = 8.46, p < .001$) and education level ($F(2, 54) = 10.38, p < .0005$), with the participants in the post-peak condition being the youngest and least educated and the participants in the pre-peak condition being the oldest and most educated, simple effects analysis indicated that within each Encoding Time, the two drug conditions did not differ in age or education level. Means (and SDs) for these control variables are illustrated in Table 4 as a function of Drug Group and Encoding Time.

Pre-Drug Cognitive Functioning. Pre-Drug measures of vocabulary, immediate and delayed episodic memory, subjective sedation, and objective sedation were analyzed with a series of 2 x 3 (Drug Group x Encoding Time) ANOVAs to determine if the six groups were equivalent prior to the drug administration. There were no significant effects of Drug Group or Encoding Time on any of the pre-drug cognitive measures. Means (and SDs) for the pre-drug cognitive measures are displayed in Table 5 as a function of Drug Group and Encoding Time.

Table 4: Means (and SDs) on the Control Measures as Functions of Drug Group and Encoding Time.

Encoding Time (min. post-drug administration)	Drug Group					
	Placebo (n = 30)		Oxazepam (n = 30)			
	Pre-Peak	Peak	Post-Peak	Pre-Peak	Peak	Post-Peak
	100	170	240	100	170	240
Age	23.60 (4.48)	21.60 (2.46)	19.60 (2.10)	23.30 (3.09)	23.10 (4.86)	19.00 (1.41)
Education Level - yrs. Post-secondary education	5.00 (2.75)	2.80 (1.92)	2.00 (1.56)	4.30 (2.75)	4.10 (1.91)	1.60 (1.26)
Body Mass Index - weight (kg)/height(m) ²	23.31 (1.11)	22.46 (1.70)	22.39 (1.21)	21.76 (2.73)	22.24 (1.88)	22.19 (2.52)
Alcohol Problems - Brief MAST Scores	.00 (.00)	.00 (.00)	1.00 (2.11)	.40 (.84)	.30 (.67)	.60 (.97)
Drug Problems - DAST Scores	1.60 (1.50)	1.80 (2.48)	1.60 (1.66)	1.20 (1.32)	1.00 (1.15)	1.20 (1.55)
Alcohol Use - Drinks Per Week	4.86 (4.66)	4.78 (4.34)	9.10 (6.14)	6.97 (9.90)	3.75 (2.56)	4.67 (2.55)
Gender Composition -% female	50	30	80	60	50	50

MAST = Michigan Alcohol Screening Test (Pokorny et al., 1972); DAST = Drug Abuse Screening Test (Skinner, 1982)

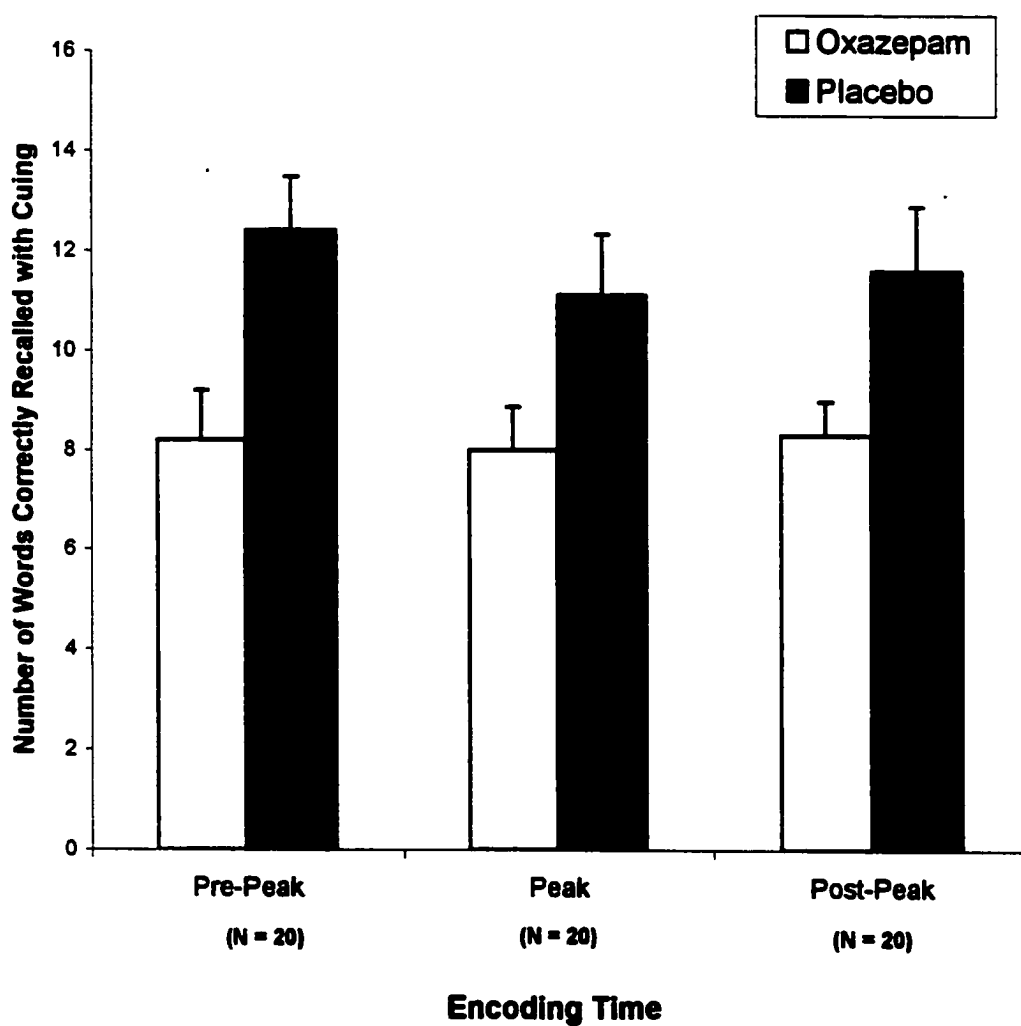
Table 5
Means (and SDs) on the Pre-Drug Measures of Cognitive Functioning, as Functions of Drug Group and Encoding Time.

Encoding Time (min. post-drug administration)	Drug Group			
	Placebo (n = 30)		Oxazepam (n = 30)	
	Pre-Peak	Peak	Post-Peak	Peak
	100	170	240	170
				240
Immediate Memory				
-WMS-R Logical Memory - IM	26.30 (7.7)	24.10 (8.94)	23.70 (4.47)	22.70 (7.38)
Delayed Memory				
-WMS-R Logical Memory -DM	23.90 (7.16)	21.00 (9.92)	21.00 (4.78)	17.10 (8.41)
Vocabulary Knowledge				
-SIL Vocabulary Test Score	31.10 (4.07)	31.70 (7.86)	31.90 (6.84)	30.50 (4.40)
Subjective Sedation				
-Mean VAS rating	43.16 (12.18)	43.12 (11.75)	43.41 (12.90)	52.80 (16.12)
Objective Sedation				
-Mean ITI (msec) on FTT	201.58 (25.14)	256.13 (131.70)	213.00 (23.85)	206.30 (49.71)

WMS-R = Wechsler Memory Scale - Revised (Wechsler 1987); SIL = Shipley Institute of Living Scale (Shipley 1940); Subjective Sedation = Mean of five 0-100 visual analogue scales (VASs) of subjective sedation (Danion et al. 1989); Objective Sedation = Mean inter-tap interval (ITI) in msec, on Finger Tapping Test (FTT; Frith 1967).

Explicit Memory. Performance on the cued recall test was scored as the total number of word stems correctly completed with target words remembered from the encoding task. Separate one-way (Drug Group) ANOVAs were conducted on the cued memory scores at each Encoding Time. The number of targets correctly recalled on the cued recall test are shown in Figure 8 as functions of Drug Group, at each of the three Encoding Times. Although direct comparisons could not be made, the placebo-treated participants appeared to correctly recall fewer targets at the peak and post-peak testing times than at pre-peak (see Figure 8). At the pre-peak testing time, the ANOVA revealed a significant main effect of Drug Group ($F(1,18) = 8.36, p < .01$). At the peak testing time, the ANOVA revealed a marginally significant main effect of Drug Group ($F(1,18) = 4.26, p = .05$). At post-peak, the ANOVA again revealed a significant effect of Drug Group ($F(1,18) = 5.09, p < .05$). At each of the three Encoding Times, the placebo group correctly completed more word stems than the oxazepam group.

Figure 8: Explicit Memory Performance: Mean Number of Words Correctly Recalled on the Cued Recall Test as a Function of Drug Group at each Encoding Time. Bars represent standard errors.



Implicit Memory. The implicit memory test was scored as the number of primed word stems and unprimed word stems which were completed with target words. Implicit memory scores were analyzed separately at each Encoding Time using a 2 x 2 (Drug Group x Priming Level) ANOVA with repeated measures. The number of stems completed with target words is shown in Figure 9 as functions of Drug Group and Priming Level, at each of the three Encoding Times. Although direct comparisons could not be made, the placebo-treated participants again appeared to complete fewer primed stems with targets at the peak and post-peak encoding times than at the pre-peak encoding time (see Figure 9). At pre-peak, the ANOVA indicated a main effect of Priming Level ($F(1,18) = 64.12, p < .001$) with primed word stems being completed with targets more often than unprimed stems. There was no significant effect of Drug Group ($F(1,18) = 2.43, n.s.$) or significant Drug Group x Priming Level interaction ($F(1,18) = .20, n.s.$). At peak testing time, the results indicated a significant main effect of Priming Level ($F(1,18) = 50.00, p < .001$) with primed word stems being completed with targets more often than unprimed stems. There was no significant effect of Drug Group ($F(1,18) = 2.90, n.s.$), but a significant Drug Group x Priming Level interaction ($F(1,36) = 4.50, p < .05$) did emerge. To further investigate the interaction at the peak testing time, simple effects of Drug Group were examined at each level of Priming. For the unprimed word stems, there was no simple main effect of Drug Group ($F(1,18) = .05, n.s.$), suggesting that drug administration did not affect participant's chance performance in generating unprimed targets. However, for the primed stems there was a marginally significant simple main effect of Drug Group ($F(1,18) = 4.17, p = .05$) with the placebo group completing more primed stems with targets than the oxazepam group. An index of the

amount of priming was calculated for each Drug Group by dividing the group's overall performance on the primed stems by its performance on the unprimed stems. In comparing these indices, it can be seen that completion of primed stems with targets was over 3 times chance levels in the placebo group, but only 2 times chance in the oxazepam group (see Figure 10). It should be noted that no statistical comparisons were performed on these priming index scores. They are displayed in Figure 10 as a function of Drug Group and Time Point for illustrative purposes only.

At the post-peak testing time there was a significant effect of Priming Level ($F(1,18) = 56.69, p < .001$) with primed word stems being completed more often with targets than unprimed stems. There was again no significant main effect of Drug Group ($F(1,18) = 2.62, n.s.$). Although the pattern of word-stem completion means observed at the post-peak testing time was similar to that seen at the peak testing time (see Figure 9), the Drug Group x Priming Level interaction showed only a trend toward statistical significance at the post-peak testing point ($F(1,18) = 2.91, p = 0.1$).

Figure 9: Implicit memory performance: Mean number of word stems completed with target on the word stem completion test as a function of Drug Group and Priming Level at each Encoding Time. Bars represent standard errors.

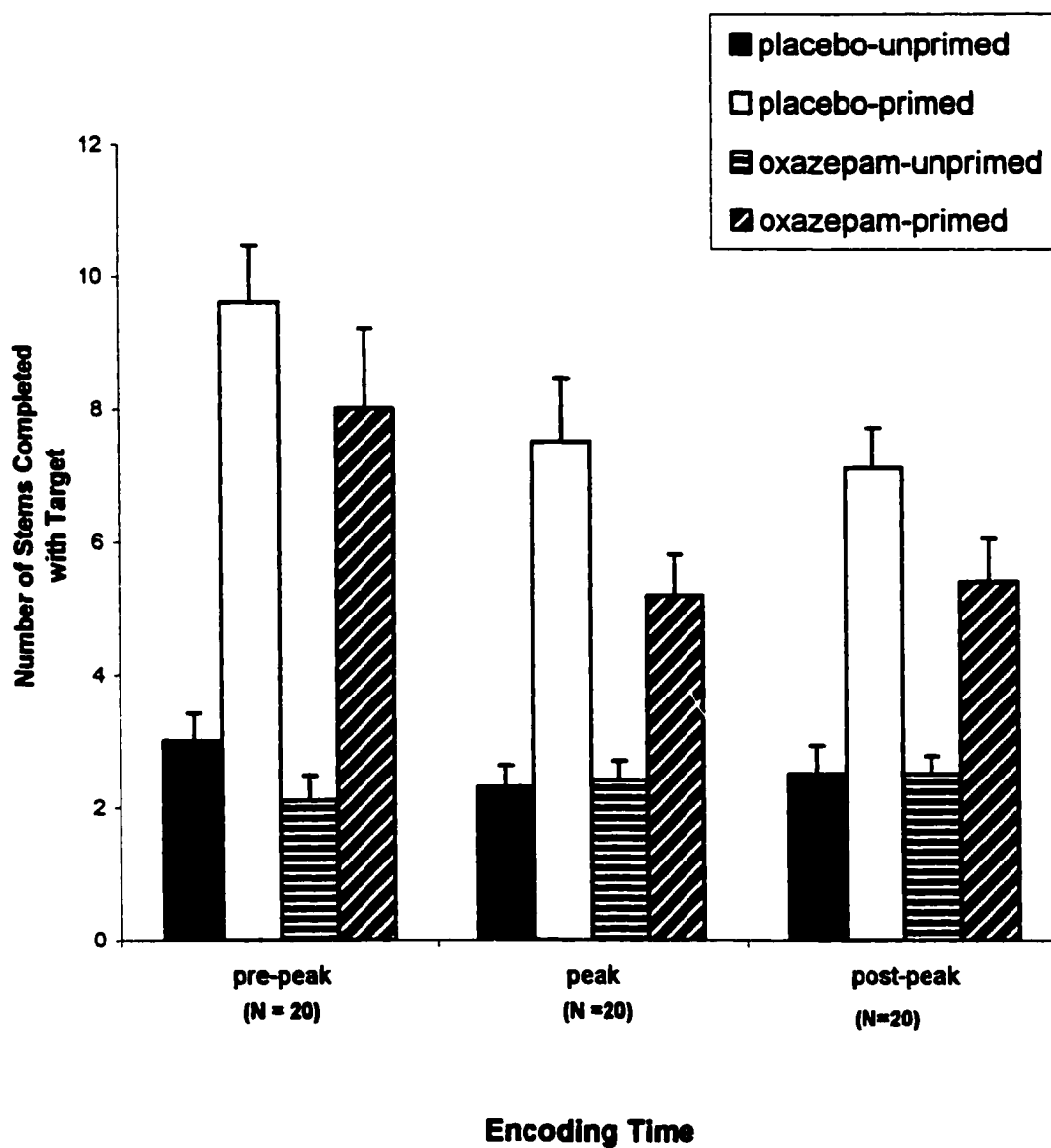
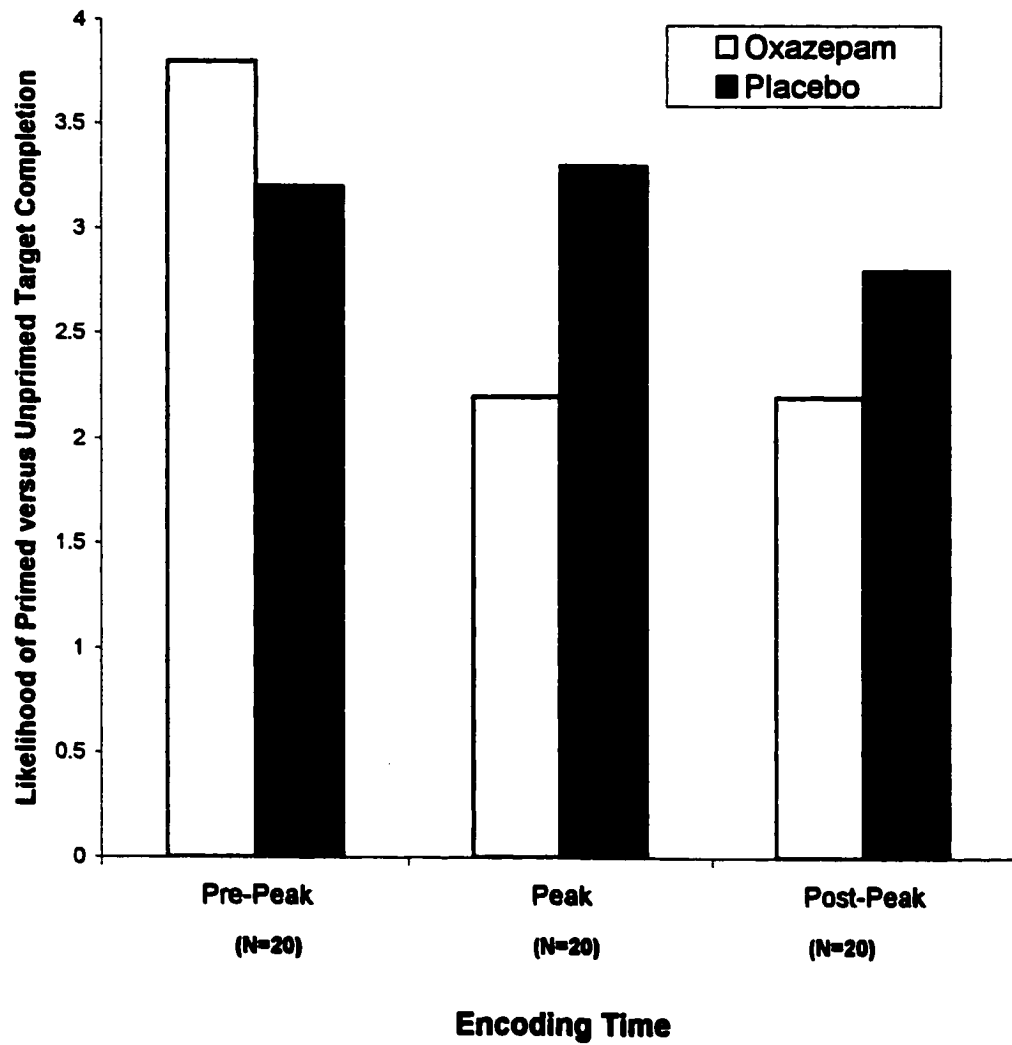


Figure 10: Amount of priming (above chance levels), as a function of Drug Group and Encoding Time.



Subjective Sedation. The effects of drug administration on subjective sedation were analyzed with a 2 x 3 x 2 (Drug Group (oxazepam versus placebo) x Encoding Time (pre-peak versus peak versus post-peak) x Drug Phase (pre versus post drug) ANOVA with repeated measures on the VAS subjective ratings. The analysis revealed no significant main effects of Drug Group ($F(1,54) = .81, n.s.$) or Encoding Time ($F(1,54) = .22, n.s.$). There was a significant main effect of Drug Phase ($F(1,54) = 32.84, p < .001$). This main effect was due to participants' reporting greater sedation at the post-drug test phase as compared to pre-drug test phase (see Table 6a). There was also a significant interaction of Drug Group x Drug Phase ($F(1,54) = 16.70, p < .001$). Simple effects tests indicated that this interaction was due to the oxazepam group reporting significantly more sedation after drug administration than before drug administration ($F(1,54) = 48.19, p < .001$), while the placebo group did not report any significant change in sedation from pre to post drug administration ($F(1,54) = 1.35, n.s.$) (see Table 6a). There were no interactions involving the Encoding Time factor.

Objective Sedation. The number of items correctly completed in 90 seconds on the Digit Symbol Task was analyzed with a 2 x 3 ANOVA (Drug Group x Encoding Time). The ANOVA indicated a significant main effect of Drug Group ($F(1,54) = 11.60, p < .01$). There was no significant main effect of Encoding Time ($F(1,54) = 1.88, n.s.$) or significant interaction ($F(2,54) = .67, n.s.$). The main effect of Drug Group was due to the placebo group correctly completing more items than the oxazepam group (see Table 6b).

Attention. Comparison of the participants' forward and backward scores on the Digit Span Test was used as a measure of post-drug attention. The forward and backward scores were each submitted to separate 2 x 3 ANOVAs (Drug Group x Encoding Time).

The results of the analysis on the forward scores revealed no significant main effect of Drug Group ($F(1,54) = 2.72$, n.s.) (see Table 6c) or Encoding Time ($F(1,54) = 2.09$, n.s.). There was also no significant interaction of Drug Group x Encoding Time ($F(2,54) = .18$, n.s.). The results of the analysis of the backward scores revealed a significant main effect of Drug Group ($F(1,54) = 5.83$, $p < .05$) which was due to the oxazepam group correctly repeating fewer digits in the backward order than the placebo group (see Table 6c). There was no significant main effect of Encoding Time ($F(1,54) = .00$, n.s.) nor was there a significant interaction of Drug Group x Encoding Time ($F(2,54) = .95$, n.s) for the Backward scores.

Table 6a, b, c

Means (and SDs) on the Measures of: a. Subjective Sedation, b. Objective Sedation and c. Attention, as Functions of Drug Group.

	Drug Group	
	Placebo (n=30)	Oxazepam (n=30)
a. Subjective Sedation		
Pre-Drug - Mean VAS rating	49.29 (15.1)	43.23 ^a (11.9)
Post-Drug - Mean VAS rating	52.84 (14.9)	64.47 ^a (15.8)
b. Objective Sedation		
Post-Drug - Mean Digit Symbol Task score	66.66 ^b (8.4)	58.90 ^b (9.4)
c. Attentional Measures		
Digit Span Forward - Number of digit sets remembered	9.70 (1.7)	8.77 (2.6)
Digit Span Backward - Number of digit sets remembered	8.33 ^c (2.3)	6.90 ^c (2.1)

Subjective Sedation = Mean of five 0-100 visual analogue scales (VASs) of subjective sedation (Danion et al., 1989); Objective Sedation = Post-Drug Digit Symbol Task (Wechsler, 1981) score. Attention = difference between the participants' forward and backward scores on the Digit Span Test. Means with similar superscripts are significantly different from one another (^ap<0.001; ^bp<.01; ^cp<.05).

Covariation Between Cognitive Impairments and Performance of Memory Tasks. A series of Analyses of Covariance (ANCOVAs) were conducted which covaried out subjective sedation (both change and post-drug scores), objective sedation, and attention, from explicit memory task scores (cued recall) at each Encoding Time, and from the implicit memory task scores (word-stem completion) at the peak testing time. As significant Drug Group differences on the implicit task were only found at the peak testing time, ANCOVAs were performed only at this Encoding Time. For the ANCOVAs involving subjective sedation, change from pre-drug baseline to post-drug testing time and post-drug subjective sedation scores on the VAS were both used as covariates to maintain consistency with Study 1. For the ANCOVAs involving attention, change from the forward to backward DST score was used as the covariate.

Explicit Memory. Covarying change in subjective sedation and post-drug sedation scores did not affect the pattern of results on the explicit memory task at the pre-peak ($F(1,17) = 8.10, p < .01$; $F(1,17) = 8.23, p < .01$, respectively), peak ($F(1,17) = 5.25, p < .05$; $F(1,17) = 5.55, p < .05$, respectively) and the post-peak testing times ($F(1,17) = 5.33, p < .05$; $F(1,17) = 5.13, p < .05$). Covarying objective sedation and attention did not affect the pattern of Drug Group differences or the significance levels of the Drug Group effects on the cued recall task at the pre-peak ($F(1,17) = 8.15, p < .01$; $F(1,17) = 7.36, p < .01$, respectively) or peak testing times ($F(1,17) = 3.60, p = .07$; $F(1,17) = 5.00, p < .05$, respectively). However, at the post-peak testing time, the Drug Group effect on cued recall appeared to be reduced both when controlling for Drug Group differences in objective sedation ($F(1, 17) = 2.28, p = 0.1$) and when controlling for Drug Group differences in attention ($F(1, 17) = 2.90, p = 0.1$). The pattern of results remained

consistent in both cases, with oxazepam-treated participants continuing to demonstrate marginally poorer explicit memory (cued recall) performance than placebo-treated participants.

Implicit Memory. Covarying change in subjective sedation and post-drug subjective sedation scores did not affect the interaction between Drug Group x Priming Level on implicit memory performance at the peak testing time ($F(1,17) = 4.50, p < .05$; $F(1,17) = 5.56, p < .05$, respectively). Likewise, covarying objective sedation and attention did not affect the pattern of results or significance levels of the Drug Group x Priming Level interaction ($F(1,17) = 4.52, p < .05$; $F(1,17) = 4.45, p < .05$, respectively) on implicit memory performance at the peak testing time.

Relation Between Word Stem Completion and Cued Recall. For each participant, a priming index was calculated by subtracting the number of unprimed word stems completed with target words from the number of primed target completions. These priming scores were then correlated with the number of correctly remembered targets on the explicit task to determine if performance on the implicit and explicit tasks were inter-related. The resulting correlation coefficient was positive and significant but relatively small in magnitude ($r = .298, p < .05$, two-tailed test) indicating that performance on the implicit task was related to, but relatively independent of, performance on the explicit task.

To assess whether the encoding instructions given to participants had any effect on the relation between word-stem completion and cued recall performance, the covariance between the priming index and explicit task scores was examined for the participants who received the incidental learning instructions (pre-peak) and again for all participants who received intentional learning instructions (peak and post-peak). At pre-peak (incidental

learning instructions) the resulting correlation coefficient was positive but not significant ($r = .252$, n.s., two-tailed test). For participants who received the intentional learning instructions (peak and post-peak) the resulting correlation coefficient was positive and significant but relatively small in magnitude ($r = .326$, $p < .05$, two-tailed test). The difference between the two correlation coefficients was non-significant ($z = .30$, n.s.) indicating that the instructions given to the participants at encoding did not have a significant effect on the degree of relation between their performance on the implicit and explicit memory tasks.

Correlations of Age and Education Level With Memory Performance. As a significant effect of Encoding Time on age and education level occurred in the analysis of the demographic variables, age and education level were correlated with indices of performance on the explicit and implicit memory tests respectively. These correlations indicated that there was no significant relationship between age and word-stem completion performance (priming index scores) ($r = .046$, n.s., two-tailed test) or between age and cued recall performance ($r = -.012$, n.s., two-tailed test). Likewise, there was no significant relationship between education and word-stem completion performance ($r = .051$, n.s., two-tailed test) or between education and cued recall performance ($r = .027$, n.s., two-tailed test).

Discussion

Overall, this study supports the hypothesis that BZs have a time-dependent effect on implicit memory processes. At 100 minutes after drug administration (pre-peak), oxazepam did not impair priming on the word stem completion task, relative to placebo. At 170 minutes after drug administration (i.e., close to oxazepam's theoretical peak),

oxazepam impaired priming on the implicit memory task, compared to the placebo group. At 240 minutes after drug administration (post-peak), oxazepam's effects on priming were only marginally significant relative to placebo. This finding of oxazepam-induced implicit memory impairments close to the theoretical peak oxazepam levels should be replicated given the increased possibility of Type I error due to the multiple analyses performed in the present study.

Completion of stems with targets was about two times chance in the oxazepam group as compared to over three times chance in the placebo group, at the encoding time closest to oxazepam's theoretical peak (i.e. 170 mins post-drug). It is interesting to note that the magnitude of priming impairment attained with oxazepam at the peak testing point in the present study is very similar to that obtained with lorazepam at the testing time closest to lorazepam's theoretical peak (i.e. 100 mins post-drug) in the Stewart et al. (1996) study: completion of stems with targets was less than two times chance in their lorazepam group as compared to over three times chance in their placebo group (Stewart et al., 1996). The results of Study 1 further showed that although both oxazepam and lorazepam significantly impaired implicit memory relative to placebo, the magnitude of priming impairment attained with oxazepam tended to be greater than that with lorazepam (i.e., lower priming odds in oxazepam vs. lorazepam of two versus two-and-a-half times chance, respectively) at 170 mins post-drug which is close to theoretical peak for oxazepam but post-peak for lorazepam.

Due to their use of repeated memory testing with the same participants, some previous studies demonstrating time-dependent effects of BZs on implicit memory task performance (e.g., Legrand et al., 1995) may have suffered from possible explicit

contamination of the implicit memory task (Roediger & McDermott, 1993). In contrast, participants in the present study were tested on the two memory tasks only at one Encoding Time, thereby reducing the potential for explicit memory contamination of the word stem completion task. Thus, the most salient explanation for the present implicit memory findings is that when oxazepam is nearing its peak blood concentration it begins to exert impairments on implicit memory processes and that oxazepam-induced priming impairments begin to wane following theoretical peak plasma concentrations.

These findings with oxazepam also lend support to the idea that BZ-induced implicit and explicit memory impairments have different time courses: explicit memory impairments seem to be apparent at an earlier time-point than implicit memory impairments (cf., Stewart et al., 1996); and explicit memory impairments appear to persist longer than implicit memory impairments (cf., Fleishaker et al., 1995). The range of oxazepam's plasma elimination half-life is 4 to 15 hours and half-life is the most important predictor of the persistence of drug effects following their onset (Greenblatt et al., 1981). Given that the post-peak testing time in the present study occurred at 240 min. (i.e., 4 hours) post-drug administration, it is possible that plasma levels of oxazepam were beginning to wane by the post-peak testing time. Thus, the present findings could suggest that oxazepam-induced implicit memory impairments depend on relatively higher levels of oxazepam in the bloodstream than explicit memory impairments. This explanation would imply that testing implicit and explicit memory even further along this drug's time course would reveal complete elimination of oxazepam-induced priming impairments prior to complete elimination of oxazepam-induced cued recall impairments (see Fleishaker et al., 1995 for such a result with alprazolam). In the future, the effects of oxazepam on implicit

and explicit memory should be tested at Encoding Times later than 240 min. post-drug, to determine if the implicit impairments continue to wane and become non-existent before the explicit impairments disappear, and to determine precisely how long explicit impairments persist. Additionally, the neural mechanisms underlying the differential impairment curves for oxazepam's effects on explicit versus implicit memory processes remain to be determined. Just as has been speculated with respect to lorazepam's consistent impairments of implicit memory (Curran et al., 1987; Knopman, 1991; Sellal et al., 1992; Curran & Gorenstein, 1993), it could be that a different population of BZ receptors uniquely affected by high blood concentrations of various BZs is responsible for priming, as opposed to explicit memory, impairments.

Although direct comparisons could not be made across Encoding Times due to the differing encoding instructions employed (i.e., incidental vs. intentional encoding), a trend was noted for the placebo participants at the pre-peak testing point to show better performance on both the explicit and implicit memory tasks relative to the placebo participants at the peak and post-peak testing points. Similar effects were noted by Stewart et al. (1996), using a within-subjects design, which they attributed to the use of repeated memory testing (i.e., learning from the first testing cycle interfering with learning in the second cycle). The fact that this effect was also observed in the present between-subjects design suggests alternatively that the decrement may represent a fatigue effect: peak and post-peak participants had to wait from 3 to 4 hours post-drug before they were given the encoding task, as compared to the 1.5 hour wait in the pre-peak condition. The trend toward superior memory performance in the pre-peak versus peak and post-peak placebo groups should not, however, compromise the interpretation of the present data

set, since separate comparisons were always made between oxazepam and the corresponding placebo control group at each Encoding Time.

In contrast to some previous studies (e.g., Legrand et al., 1995; Fleishaker et al., 1995), the memory tasks used in the present study met the retrieval intentionality criterion and, therefore, could be compared directly (Roediger & McDermott, 1993). Moreover, the possibility of explicit contamination of the implicit task was reduced by consistently administering the implicit task prior to the explicit task, as recommended by Roediger and McDermott (1993). The possibility still remains that the explicit test may have been contaminated by implicit processes because memory testing was within-subjects (Roediger & McDermott, 1993). However, research has shown that using perceptual priming tasks (e.g. word-stem completion task) as opposed to conceptual priming tasks (see discussion of conceptual and perceptual priming in the General Discussion) greatly decreases the likelihood of implicit contamination of the explicit test (Roediger & McDermott, 1993). In addition, the word-stem and cued-recall tasks demonstrated less than 10% shared variance in the total sample. If contamination of one task by the other had occurred, one would expect greater than 10% shared variance between the tasks.

Finally, it could be argued that use of the intentional learning instructions at the peak and post-peak testing points, by preparing participants for upcoming memory testing, caused them to “catch on” to the true purpose of the word stem completion task more than participants tested at the pre-peak (incidental learning instructions) testing point. This argument would imply significantly greater explicit contamination of the implicit task at the peak and post-peak testing points than at the pre-peak point. Consistent with this possibility, the correlation between performance on the implicit and explicit task was

significant ($p < 0.05$) for participants tested at peak and post-peak (i.e., those who received intentional learning instructions), but was not significant for those tested at pre-peak (i.e., those who received incidental learning instructions). However, the difference between these correlations did not even approach significance, indicating that the degree of explicit contamination of the implicit task was not different for those who had received intentional as opposed to incidental instructions at encoding.

One of the consistent difficulties when studying medication side effects is that most drugs have more than one effect. In addition to memory impairment, BZs have many other effects on cognitive processes (Curran, 1986). In the present study the oxazepam-treated participants reported more sedation than the placebo participants. The oxazepam participants also showed significant levels of objective sedation on the Digit-Symbol Task, as compared to the placebo participants. In addition, oxazepam-treated participants showed impaired performance on an attentional measure (i.e., impairments relative to placebo on the Backward, but not Forward, component of the Digit Span Test; Lezak, 1995). This is an important finding because several other researchers have failed to measure attention in their studies (e.g., Curran & Gorenstein, 1993; Legrand et al., 1995; Stewart et al., 1996) and because it extends some previous findings of BZ-induced attentional impairments (see review by Curran, 1991) to a novel attentional measure that taps attentional encoding. Given these oxazepam-induced attentional impairments, it is possible that drugged participants in previous studies had difficulty attending to the encoding lists, as compared to the placebo participants. Therefore, the memory impairments found in such previous studies could have been secondary to attentional impairments.

In an attempt to rule out the possibility that the impairments in subjective sedation, objective sedation, and/or attention were primarily responsible for the memory impairments in the current study, a series of analyses of covariance (ANCOVAs) were performed. These ANCOVAs indicated that none of these additional cognitive factors influenced the Drug Group effect on the implicit task observed at the peak Encoding Time. Likewise, subjective sedation did not affect the Drug Group differences on the explicit task. However, at the post-peak testing point, the significant Drug Group effect on the cued recall task was reduced to marginal significance when attention task performance and objective sedation were used as covariates. Therefore, it appears that attention and objective sedation did have some contribution to BZ-induced performance impairments on the explicit task (cf., Bishop & Curran, 1995). Specifically, attention and objective sedation appeared to contribute to BZ-induced explicit memory impairments when the blood concentration of the drug was declining. This finding is also consistent with previous findings that divided attention reduces explicit memory performance while leaving priming intact (Rabinowitz et al., 1982). Moreover, the fact that attention and objective sedation contributed to cued-recall performance but did not influence priming once again indicates that explicit and implicit memory processes are dissociable (Roediger & McDermott, 1993).

To date four BZs -- diazepam (Legrand et al., 1995), lorazepam (Curran & Gorenstein, 1993), alprazolam (Fleishaker et al., 1995) and oxazepam (Stewart et al., 1996) -- have been found to impair priming. In each of these studies, as in Study 1 and 2 of the present thesis, the results are consistent with the idea of time-dependent effects of BZs on memory. In the future, the effects of different BZs on memory task performance

need to be studied at testing times prior to, close to, and following peak blood concentrations for the BZ in question to determine if the time-dependence hypothesis is supported, and to develop a better understanding of the relative implicit and explicit memory impairment curves over time, for each drug. In addition, different doses of each BZ should be studied to determine how dosage interacts with the memory impairment curves for implicit and explicit memory.

It is important to determine the relative time courses of BZ-induced implicit and explicit memory impairments for both theoretical and clinical reasons. Theoretically, findings such as those of the present study indicating differential impairment curves over time suggest that performance on the explicit (cued recall) and implicit (word stem completion) memory tasks are subserved by different memory systems (cf. Schacter, 1994). Clinically, knowledge of precisely when implicit and explicit memory impairments occur relative to drug administration could be useful for anaesthetists who wish to take advantage of these amnestic effects in the context of BZs as surgery pre-medicants (Curran, 1991). Such knowledge would also likely be helpful to the psychotherapist who wishes to minimize the impact of these potentially adverse side effects for their clients who are concurrently receiving psychotherapy and BZ therapy for the treatment of an anxiety disorder (Westra & Stewart, 1998).

CHAPTER FIVE

Implicit and Explicit Memory: Developmental Considerations

The results of Studies 1 and 2 provide evidence supporting the hypothesis that there are time-dependent effects of BZs on both implicit and explicit memory processes. The fact that the time course of the impairments appears to differ for explicit vs. implicit memory task performance, provides further evidence that these are theoretically and empirically distinct memory processes. Moreover, as noted previously, knowledge about time-dependent explicit and implicit memory impairments induced by BZs might have clinical relevance for individuals who are using BZs in applied settings. Certainly, these time-dependent effects might be detrimental for anxiety-disordered clients who are engaged in cognitive-behavioural therapy and who are concurrently taking BZs (Westra & Stewart, 1998). However, one situation in which the time-dependent amnesic effects of BZs may actually be beneficial is when they are administered before surgery, as pre-operative medicants. The purpose of Study 3 (see Chapter 6) is to extend the lab-based findings of Studies 1 and 2 to an applied setting in which BZ amnesic effects may be beneficial for users – that is, in a pediatric day-surgery setting, where BZs are often administered as preoperative medicants. However, before designing a study to investigate the time-dependent effects of BZs in children, a review of the literature was conducted to answer the following questions:

- 1) Do implicit and explicit memory processes theoretically exist in children?
- 2) At what age are implicit and explicit memory reliably observed?

3) Are there existing explicit and implicit memory tasks: (a) that are developmentally appropriate for children; and (b) that meet the retrieval intentionality criterion (Schacter et al., 1989) allowing for their direct comparison? Also, if there are not such tasks available, are there existing tasks that could be readily modified to achieve the above two goals?

Studies of Implicit and Explicit Memory in Children

Researchers have been studying explicit memory in children for more than 100 years. In 1894, Kirkpatrick noted that free recall skills improved significantly as children got older. Since that time numerous studies have verified developmental improvements in explicit memory in children (e.g., Brown, 1975; Chi, 1978; Flavell, 1977). Studies indicate that young children are less likely than older children to use mnemonic strategies such as rehearsal and chunking when asked to memorize information (see review by Dempster, 1981), likely contributing to the above-noted, age-related differences in explicit memory performance.

Memory theorists (e.g., Tulving, 1987) have suggested that implicit memory develops before explicit memory, and that unlike explicit memory, implicit memory is stable over the life span. In fact, there is some evidence that implicit memory may exist even before birth: newborns have been shown to prefer speech passages that were read aloud during their last month in the womb, as compared to novel passages (DeCasper & Spence, 1986). Nonetheless, relatively little empirical work has been conducted on implicit memory in children. Little over a decade ago, Schacter (1987) noted that virtually no empirical studies of implicit memory in children had been conducted. He

suggested that if implicit and explicit memory can be dissociated developmentally, it would lend additional support to the idea that they are distinct memory processes.

In 1985, Carroll, Byrne, and Kirsner conducted what is believed to be the first direct investigation of implicit memory in children. Groups of 5-year-olds, 7-year-olds, and 10-year-olds were initially shown a series of pictures and asked to either search for a cross hidden on each picture (shallow [perceptual] encoding) or judge the portability of each item (deep [semantic] encoding). Next, each of the children was presented with 25 new pictures and 25 pictures that they had already encoded. Half of the children were given a recognition task (explicit memory) and asked to indicate if they had seen the picture previously. The remaining children were given an implicit memory task in which they were asked to name the object depicted in each picture; “savings” were used as a measure of priming on this task. Savings are defined as the difference between the time taken to name the pictures that had been previously encoded (primed) and the time taken to name the novel pictures (unprimed). The results of the recognition task indicated that explicit memory was better in the older children. Overall, the five-year-olds only recognized 51% of the previously encoded items (i.e., performed at chance levels), while the 7 and 10 year old children recognized 78% and 83%, respectively. On the implicit naming task, all children named the primed stimuli faster than the unprimed stimuli, indicating that the task was an effective measure of implicit memory. In contrast to the explicit task, there was no developmental age progression of performance on the implicit task, with each of the age groups showing similar savings. In addition, the depth of encoding (shallow vs. deep) affected the recognition data (deeply encoded pictures were remembered better), but had no effect on implicit memory. Overall, the results suggest

that explicit memory skills improve as children get older, while implicit memory is evident even in younger children and remains stable over the childhood years. However, in this study, implicit and explicit memory were not directly compared using the same participants, making the evidence for this conclusion less convincing.

In a similar study (Lorsbach & Morris, 1991), second and sixth grade children were first asked to name pictures as quickly as possible. The next day, the test was repeated with a combination of new and previously encoded pictures. The results indicated that all participants showed significant savings in the naming of the previously encoded pictures (i.e., significantly faster picture naming speeds for the primed versus unprimed pictures). In addition, the two age groups showed a similar amount of savings. After the implicit task, the children were again shown each picture and asked if it was one of the pictures that they had previously encoded the day before (recognition memory). On this task a significant effect of age was found, with older children showing better recognition performance. Again, this study is supportive of the hypothesis that implicit memory is stable across the lifespan whereas explicit memory shows developmental improvement.

In another study (Ellis, Ellis, & Hosie, 1993), 5-, 8-, and 11-year-old children encoded a series of pictures of classmates and were asked to identify the gender of each. Next, they were shown 10 pictures of classmates that they had seen previously, interspersed with 10 pictures of classmates that had not been previously encoded. In addition, pictures of children unknown to the child were also included. Children were asked to press one computer key if they knew the child, and another if the child was unfamiliar. Comparison of the reaction times for the primed and unprimed familiar faces

indicated that all age groups showed a priming effect. In fact, the group of 5 year olds showed more savings (i.e., faster reaction time for primed versus unprimed pictures) than the older children, although this finding is most likely due to the slower reaction times of 5 year olds to unprimed faces giving them more room for improvement when shown primed pictures.

A difficulty with studies of memory development in children is that memory does not develop in isolation from the development of other skills including language, reaction speed, perception, problem solving, and comprehension (Brown, 1971). As noted by Parkin (1997), implicit memory tasks that measure reaction time (such as the tasks used in the above studies by Carroll et al., 1985, Lorsbach & Morris, 1991, and Ellis et al., 1993) are not recommended for use with child research participants, as there are significant developmental increases in reaction time which may interfere with the data, and make interpretation difficult (as seen in the Ellis et al., 1993 study).

Another difficulty with the above studies is that the use of savings as a measure of priming leads to a high probability of explicit contamination of the implicit task (Naito & Komatsu, 1993). This is because the implicit task actually involves presenting the encoded stimuli for a second time, making it very likely that participants will “catch on” and begin to use explicit memory strategies to facilitate performance (e.g., “I saw the picture of a bunny and a chicken before. I bet she’s going to show the picture of the bear soon”). In addition, it is possible that older children would be more likely to “catch on” and use explicit strategies, while younger children might continue to use implicit strategies. Therefore, developmental differences in implicit memory might not be adequately tested in the above studies. However, the data in the above studies are not

consistent with this speculation, as the older children with better explicit memory performance were not superior to the younger children on the implicit memory tasks. Therefore, it is probable that the older children were not more likely to be using explicit memory strategies on the implicit memory tasks.

In 1988, Parkin and Streete attempted to study implicit memory in children using a picture completion task. The researchers compared three groups of children (aged 3, 5, and 7 years) and an adult group. The results indicated that all age groups showed evidence of implicit memory. In contrast to most previous studies suggesting no developmental improvements in implicit memory performance, initial analysis of the Parkin and Streete (1988) results indicated increased savings with age. However, when the savings score was calculated as a proportion of each child's initial score, there was no significant difference between the age groups. The authors suggested that the initial findings were confounded by the fact that the age groups had different levels of initial performance (i.e., a mean identification score of 1.77 and 2.61 for 3 and 7 year old children, respectively).

The Parkin and Streete (1988) study has serious methodological flaws, which makes interpretation of the results difficult. Typically, in the adult literature, individuals are shown a series of complete pictures during the encoding period. Later, individuals are shown pictures in their most fragmented form and asked to identify them. Pictures are shown in progressively more complete form until the participant is able to identify the pictures. If a participant is able to recognize pictures in a more fragmented (less complete) form when they have seen it previously, this is considered evidence of priming (see review by Roediger & McDermott, 1993). However, in a major departure from this

standard protocol, Parkin and Streete had their child participants encode the pictures in their various fragmented forms (shown in more and more complete form until the child named the picture) and later tested their memory for these fragmented forms. This procedure is problematic for several reasons. First, the duration of exposure to the stimuli during encoding would not be held constant across participants, because those naming the picture earlier (in less complete form) would thus have less exposure to the picture than those naming the picture at later stages (in more complete form). In addition, during the test phase, the researchers stopped the participants after each identified picture and asked if the picture had been previously encoded (explicit, recognition memory task). When children were presented with fragmented pictures for a second time, it is likely that they would realize that the implicit memory task had something to do with the encoding task. In addition, once the experimenter began asking questions about memory for the encoding task the purpose of the implicit task would likely be revealed, leading to possible explicit contamination of the implicit task. However, Parkin and Streete's (1988) results indicated that explicit, recognition memory did improve with age, as compared to implicit memory, and that performance on the implicit and explicit memory tasks were not correlated. Nevertheless, the study is difficult to interpret, due to its many methodological shortcomings.

In 1990, Naito compared the performance of children in the first, third and sixth grades, in addition to a group of adults, on a word-fragment completion task. On this task, participants were presented with fragments (some letters randomly presented throughout the word such as "b_ n_" for "bank") of previously encoded words and novel words and were asked to complete each fragment with the first word that came to mind.

Her results indicated that all groups showed a significant priming effect (i.e., with primed words being correctly completed with targets twice as often as unprimed words). In addition, the size of the priming effect was the same for all age groups, again suggesting that implicit memory is relatively stable across the lifespan. In a second study, Naito again compared first graders, third graders, sixth graders and adults on a free recall task. The results indicated that the adult group recalled more words than any of the other age groups. In addition, third and sixth graders recalled significantly more words than first graders. The results of this second study indicated that explicit memory does appear to follow a developmental progression. Unfortunately, implicit and explicit memory performance was not directly compared using the same participants. It should also be noted that the word-fragment completion task is a very useful tool for investigating priming (Roediger & McDermott, 1993), but since it involves reading, it can only be used in studies of school-aged children.

More recently, DiGiulio, Seidenberg, O'Leary, and Raz (1994) compared the performance of 8- and 12-year-old children on two implicit memory tasks – fragmented pictures and degraded words. The results indicated that the 8- and 12-year-old children benefited equally from previous exposure to the primed pictures and words. In contrast, when given a free recall task for the pictures and words that had been presented earlier, the 12-year-old children remembered a significantly greater number of words and pictures than the 8-year-old children. Again, this study lends support to the stability of implicit memory across the lifespan in contrast to explicit memory, which shows developmental progression.

In a study by Perruchet, Frazier, and Lautrey (1995), grade 2 and grade 5 children encoded a list of 14 words (taken from a larger list of 28), which were presented both visually and orally. To ensure that the words were semantically encoded, the researchers asked a question about each word (e.g., “Friday – Do you go to school on Friday?”). Immediately after the encoding task, children were asked to name items in all 28 (14 primed and 14 unprimed) categories (“What is the first day of the week that comes to your mind?”). Priming occurred if children were more likely to answer the questions regarding primed categories with targets (words that they had previously encoded) than to answer questions regarding unprimed categories with targets. After completion of the implicit task, children were tested for explicit recall of the word list (“A moment ago, I showed you a day of the week. Do you remember what day it was?”). In their first experiment, there was a significant age effect on both memory tasks, suggesting that implicit and explicit memory improved with age. However, when the researchers repeated their study (experiment 2) using child-normed words with an average baseline rate (e.g., the target in the fruit category was changed from “Golden” [a type of apple] to “banana”), the findings were more consistent with previous work. Specifically, implicit memory was found to be stable across the age groups. An explicit memory task was not administered in experiment 2, however. The implicit memory results in the second experiment could not be explained by a ceiling effect, as even the oldest children did not remember/generate all words that had been previously presented during encoding. The results of these two experiments suggest that implicit memory testing with children should not use tasks that have only been normed on adults, as adult-normed words and pictures may be less familiar to the younger groups of children. These unfamiliar words

and pictures may not be as well encoded, and children will most likely have difficulty answering questions about them. Obviously, researchers in this area must be careful to choose developmentally sensitive tests of implicit and explicit memory.

In an interesting study, Bullock-Drummey and Newcombe (1995) used a developmentally appropriate version of the picture fragment completion implicit memory task that is commonly used with adults (Roediger & McDermott, 1993). In this study a group of 3-year-old children looked at a children's book containing drawings of animals, with the examiner. Next, an overhead projector was used to show the same pictures, in addition to new pictures, in blurry form. The pictures were shown in progressively less blurry form until the children named them. In addition, children were asked if they had seen the picture previously after each picture was named. Again, this is a problem because when the examiner begins to ask questions about the encoding task during implicit memory testing, children will most likely gain awareness that their memory is being tested, and may begin to use explicit strategies on the implicit task (as was noted for the Parkin & Streete, 1988 study). To assess implicit memory, the degree of focus/blurriness at which the primed vs. unprimed pictures were named was compared. Overall, the results indicated that while recognition memory was quite poor in 3-year-old children, implicit memory (priming) was intact. In a second experiment, three age groups (the same 3-year-olds from experiment 1, as well as 5-year-olds and adults) were compared on the same task. Results indicated that 5-year-old children and adults performed significantly better on the recognition task than 3-year-olds (despite the fact that the 3-year-old children had now seen the pictures twice). Again, implicit memory remained stable across age groups.

In a well-designed study of memory in young children, Greenbaum and Graf (1989) directly compared implicit and explicit memory in 3-, 4- and 5-year-olds. The children were initially shown a series of line drawings of objects that fell into one of four categories (zoo, kitchen, park, and restaurant). Previously, in a pilot test, children were asked to name items that could be seen in a zoo, a kitchen, a park, and a restaurant, respectively. Items that appeared with intermediate frequencies were used in the study. To test implicit memory, children were told a story about a boy/girl going to a certain place (zoo, kitchen, park, or restaurant) and the child was asked what the boy/girl would see in that place. To test explicit memory, children were given a cued-recall task in which they were shown the back of the cards and asked if they remembered the pictures that they had seen. Unfortunately, they were not cued to the specific categories, which would have made the implicit and explicit tasks directly comparable (satisfying Schacter et al.'s, 1989 retrieval intentionality criterion). The results of the study indicated that priming (as measured by the proportion of target words named for the primed vs. unprimed stories) occurred for all age groups, and no difference in the amount of priming occurred between the age groups. In contrast, there was a significant age-related increase in performance on the cued recall task, with the 3, 4 and 5-year-old children remembering 17%, 37% and 47% of the pictures, respectively.

A problem with each of the above studies, except for Perruchet et al. (1995), is that they fail to satisfy the "retrieval intentionality criterion" (Roediger & McDermott, 1993), meaning that the implicit and explicit tasks are not directly comparable. Certainly, future investigations of implicit and explicit memory in children should use directly comparable tasks. In addition, most of the above studies used pictures and words that

had been normed for use with adults. It is extremely important that child-normed items be used when investigating implicit and explicit memory in children. This ensures that the pictures or words are recognized and accessible to children. If an adult were given a list of completely unfamiliar words to encode, and later asked to complete word stems with the first word that came to his/her mind, it is unlikely that the adult would chose this unfamiliar word, as many other words would be much more easily accessed from the individual's memory. However, this idea has not been tested in the research literature.

Overall, the above studies lend support to the idea that implicit memory is intact in children as young as three, and that explicit memory progresses developmentally. These results are similar to studies of elderly individuals which have found that implicit memory stays relatively intact as people age, while explicit memory declines (Graf, 1990; Light & Singh, 1998). As described by Parkin (1993), the development of implicit memory across the lifespan appears to follow a "first in, last out" policy, when compared to the development of explicit memory. In other words, implicit memory develops prior to explicit memory in childhood, and explicit memory declines with aging in the elderly more than implicit memory. In addition, the results of the above studies indicate that explicit memory certainly exists in children as young as four (e.g., Bullock-Drummey & Newcombe, 1995; Greenbaum & Graf, 1989), in an amount that is readily measurable using existing tasks. Overall, it appears that it is possible to study both implicit and explicit memory in children, as long as child-normed memory tasks are used and the retrieval intentionality criterion is satisfied.

In conclusion, the present review of the research literature indicates that both implicit and explicit memory processes theoretically exist in children, and that both can

be measured in children as young as four. Although most of the above studies used “savings” as a measure of implicit memory, these tasks are not considered developmentally appropriate due to the age-related improvement in reaction time (Parkin, 1997). In addition, these tasks increase the probability of explicit contamination of the implicit task (Naito & Komatsu, 1993). As seen in Naito (1990), word-fragment completion tasks can also be used with children. However, these tasks are only appropriate for school aged children. Bullock-Drummey and Newcombe (1995) used a picture identification task that appeared to be appropriate for use with children. However, the pictures they used were taken from a well-known children’s book, increasing the likelihood that children would have already encoded the pictures. Overall, the Greenbaum and Graf (1989) methodology appears to be the most appropriate task to assess implicit memory in young children. The task has been used with children as young as three, and the categories and pictures used in the task are child-normed. Although Greenbaum and Graf (1989) did not use explicit and implicit memory tasks that satisfied the retrieval intentionality criterion (Schacter et al., 1989), this can be easily modified. Instead of asking children for their explicit memory for all pictures presented, their memory should be “cued” using specific categories (“tell me all the pictures I showed you of things you see in a restaurant”). With this slight modification, it is believed that the Greenbaum and Graf (1989) methodology should be appropriate for studying both implicit and explicit memory in young children.

CHAPTER SIX: Study 3

The Time-Dependent Effects of Benzodiazepines on Implicit and Explicit Memory in a Paediatric Surgery Setting

Early research indicated that surgical operations can be a particularly stressful experience for children. Eckenhoff (1953) reported that 32% of children who had surgery, and were hospitalized overnight, experienced problems upon returning home. Common problems included night terrors, temper tantrums, anxiety, and bed-wetting. Although it is possible that many of these problems were caused by hospitalization, as opposed to the surgery experience, further analysis of the data in the Eckenhoff (1953) study indicated that children under the age of eight who had an unsatisfactory induction of anaesthesia (crying, struggling) were twice as likely to have problems upon returning home after the hospital experience. A more recent study (Kain, Mayes, O'Connor, & Cicchetti, 1996) found that increased anxiety during the surgery experience predicted an increased incidence of negative postoperative behavioral problems, with more than 50% of children showing some negative behavioral responses within the two weeks following surgery. Anxiety also creates a problem in the hospital setting, as more than 10% of children between the ages of 3-6 years will show anxiety-related behavioral problems while at the hospital (e.g., struggling, trying to get away), causing difficulties for staff (Vetter, 1993). Also, children who are anxious or crying during anaesthesia induction are more likely than calm children to become hypoxaemic (decreased blood oxygen saturation) -- a potentially dangerous condition (Laycock & McNicol, 1988). Certainly, these results indicate that anxiety prior to, during, and after the surgery experience can

cause problems for children, parents and hospital staff, and may even be a cause of medical concern.

McKie and Thorp (1973) found an additional problem with the surgery experience that may be upsetting for children. The results of their study indicated that at least 5% of children who had undergone anaesthetic and surgery had valid memories for certain events that had happened during the surgery, when they were apparently asleep and non-responsive. For example, one child who had a dental extraction described hearing “clicking noises like something being dropped in a saucepan now and then”. In addition to the children who had specific memories, other children described “horrible dreams” during the surgery and were upset, frightened and unwilling to sleep alone when they returned home post-surgery. A recent review of the literature supported the idea that valid memories of events that occur during the surgery experience can occur (Jelicic & Bonke, 1993). Certainly it appears that the possibility of anxiety during the induction of anaesthetic, and memory for events occurring during the surgery experience can be traumatic for young children and may contribute to behavioural difficulties in the weeks following the surgery.

In the late 1970s, hospitals became interested in the possibility of day-treatment surgery for children (Steward, 1980). It was hypothesized that if children had their operations in a day surgery setting, they would not have to be separated from their family overnight, thus reducing anxiety. However, the possibility of difficult anaesthesia inductions and memory for events occurring during the surgery still remained.

Both anaesthesiologists (DeJong & Verburg, 1988) and parents (Eckenhoff, 1953) have noted that a drug that would decrease anxiety and increase sedation before the

induction of anaesthesia might be beneficial. In one study, a parent returning a post-surgery questionnaire noted "I firmly believe that if all children were given some drug to quiet them and make them good and drowsy, they would accept the anesthetic more readily" (Eckenhoff, 1953). Many anaesthesiologists (e.g., DeJong & Verburg, 1988) have noted that amnesia could also be beneficial to children having surgery, as it might attenuate the psychological difficulties associated with problematic inductions and separation from parents. In addition, DeJong and Verburg (1988) noted that upsetting memories of a previous surgery might be especially difficult for children requiring additional surgeries, and anxiety for future surgeries would be less likely if the child had little or no memory of the previous surgery experience (however, please see the discussion for another position on this matter). This issue appears particularly pertinent for types of surgery that tend to occur repeatedly for the same children (e.g., myringotomy or ear tube surgery).

In 1980, Dundee and Wilson investigated a new, water-soluble BZ, midazolam, which had just begun clinical trials in North America. The researchers administered 5 mg of intravenous (i.v.) midazolam to adult women who were undergoing minor surgery. To determine if memory was impaired by midazolam, the women were shown a series of postcards at predetermined intervals (1, 2, 3, 5, 7, 10, 15, 20, 40 and 60 min. post drug) after midazolam administration. The experimenters also made behavioral observations of the women's appearance of sedation at each of the above intervals. At 5-6 hours post-surgery, the women were given a free recall and a recognition task to measure their memory for the postcards. The results indicated that both anterograde amnesia and sedation occurred maximally when memory encoding or objective sedation ratings

occurred between 2 and 5 minutes after injection, and the effects were no longer apparent by 20 minutes post-drug. However, a limitation of the above study is that it was not placebo controlled.

Few studies have examined the effects of midazolam on implicit memory. In one laboratory-based study, adults were administered one of two doses (.05 or .10 mg/kg) of i.v. midazolam or placebo (Ghoneim, Block, Ping, El-Zahaby, & Hinrichs, 1993). Before, and at 20 minutes after midazolam administration, participants completed tasks to assess implicit memory (word-stem completion), explicit memory (free recall), objective sedation (DSST), and subjective sedation (VAS). The results indicated that both doses of midazolam increased both objective and subjective sedation, as compared to the pre-drug measures and the placebo-treated participants. In addition, midazolam impaired both implicit and explicit memory, compared to the placebo participants. Unfortunately, the explicit and implicit tasks in the Ghoneim et al. (1993) study did not meet the retrieval intentionality criterion.

In an interesting study of implicit memory after intramuscular (i.m.) administration of midazolam in adults in a clinical (surgery) context (DeRoode, Jelicic, Bonke, & Bovill, 1995), participants wore headphones during the surgery after induction of anaesthesia. All patients received i.m. midazolam (.10 mg/kg) approximately 30 minutes before the surgery. Five minutes after the anaesthetic was administered, one of two tapes was played. One group of patients heard 10 little-known, historical facts. The other participants heard a series of 10 unfamiliar names. After the patients were awake, the first group was asked a number of historical questions, half that could be answered with the information played on the tape. The other participants were given a list of 20

names (10 new, 10 old), and asked which were the names of famous people. This latter task is based on the assumption that participants with implicit memory of the primed names would be more likely to think the primed names were famous, due to their familiarity. The results indicated that there was no difference between primed and unprimed words in either of the groups, suggesting impairment of implicit memory in midazolam treated surgery patients. This is in contrast to another study conducted by the authors (Jelicic, DeRoode, Bovill, & Bonke, 1992) in which participants, who were not pre-medicated before receiving anaesthetic, showed evidence of implicit memory, using identical memory tasks, for the information provided during the surgery experience. However, these studies were not placebo-controlled, and the two studies did not use the same participants.

In the early 1990's, researchers began investigating the use of midazolam as a pre-medicant given to children before lumbar punctures (LPs) and bone marrow aspirations (BMAs). These procedures are often extremely frightening to children, and require the child to remain relatively still. Researchers have suggested that a drug that can calm children before these procedures might make the experience less aversive (Sievers, Yee, Foley, Blanding, & Berde, 1991). One study in which i.v. midazolam (.05-.15 mg/kg at the discretion of the oncologist) was administered before a BMA or LP indicated that more than 60% of children reported complete amnesia for the events which occurred during the procedure, when later asked questions such as "Do you remember the insertion of the needle?". This amnesia occurred even though the patients were awake (i.e., non-anesthetized) throughout the procedure (Sievers et al., 1991). In a similar study (Friedman et al., 1991), children were shown one picture before and another

approximately 5 min. after administration of i.v. midazolam (.2 mg/kg). Later, the children were asked to name the pictures they had been shown (free recall). If the child could not remember, he/she was asked to select the picture from a group of pictures (recognition). Unfortunately, the number of pictures shown to children in the recognition task was not reported. The results indicated that children in the midazolam and placebo groups had equivalent recall and recognition scores pre-midazolam, but only 9% of midazolam treated participants could remember the post-midazolam picture on the free recall task, as opposed to 88% of the children who received placebo. On the recognition task, the midazolam group again showed impaired performance, with only 18% of the midazolam-treated children showing correct recognition, as opposed to 100% of the placebo-treated participants. In addition, the midazolam-treated participants exhibited significantly less observer-rated distress during the procedure. In fact, anecdotal evidence indicated that some of the children did not even realize that the procedure had taken place. In a similar study, children having repeat LP/BMAs were given i.v. midazolam (.20 mg/kg) as a premedicant during one procedure, and fentanyl (a narcotic analgesic) as a premedicant for another procedure in a counter-balanced fashion. Before a third procedure, children were asked to choose the pre-medicant that they would receive. The results indicated that most children preferred midazolam to fentanyl, suggesting that amnesia for the procedure is the most desired effect (Sandler et al., 1992). In fact, most children reported that they would refuse future procedures if they did not receive the midazolam premedication (Sandler et al., 1992).

Midazolam has also been used in children who are having day surgery procedures that are not oncology-related. In one of the first studies of midazolam in a non-oncology-

related paediatric surgery context, Taylor, Vine, and Hatch (1986) administered i.m. midazolam (.2 mg/kg) to children having day-surgery. Unfortunately, no placebo group was used in this study, and the midazolam group was compared to a second group of children who received papaveretum (an analgesic sedative) and hyoscine (an anticholinergic drug used to treat nausea). Hyoscine (or scopolamine) has many cognitive side-effects including inattention, increased sedation and explicit memory amnesia (Bishop et al., 1996). Sedation was assessed, using an observer-rating scale, at several points (before medication, in the anaesthetic room post-medication, and postoperatively). Observers were blind to each child's drug group status. In addition, a picture was shown to each child in the anaesthetic room. Results indicated that the difference between the pre- and post- medication sedation scores was significantly larger for the midazolam group than the papaveretum/hyoscine group. In addition, the midazolam group was significantly less likely than the papaveretum/hyoscine group to remember the picture shown to them in the surgery room, as assessed using a free recall task. Although this study suggests that midazolam causes sedation and amnesia, there was no placebo group for comparison. In addition, the midazolam group also received atropine (an anticholinergic drug) as an additional pre-operative medicant. Although atropine is not reported to affect memory or increase sedation (Canadian Pharmaceutical Association, 1999), the addition of atropine to midazolam makes it even more difficult to interpret the results of the Taylor et al. study.

In another study, children were administered intranasal midazolam (.2 mg/kg or .3 mg/kg) or an intranasal saline placebo before a day surgery procedure (Wilton, Leigh, Rosen, & Pandit, 1988). The results indicated that observer-rated sedation (observers

were blind to the child's drug group status) scores were higher for the both the midazolam-treated groups than for placebo-treated children. In addition, 60% of the children who received placebo were rated by observers as being agitated during induction of anaesthesia, as compared to only 3% of midazolam-treated children. In another study using intranasal administration of midazolam (.20 mg/kg) (Twersky, Hartung, Berger, McClain, & Beaton, 1993), the midazolam group showed decreased ability, compared to intranasal placebo-treated participants, to recall or recognize pictures shown after, but not before, midazolam/placebo administration. These results lend further support to the idea that midazolam causes anterograde amnesia in children. In addition to i.m., i.v., and nasal administration, adequate sedation and decreased anxiety at anaesthesia induction has been shown with rectal administration of midazolam (DeJong & Verburg, 1988).

Oral Midazolam

Although i.v. and i.m. midazolam show potential as a sedative and amnestic pre-surgery medicant, studies have indicated that children describe pre-operative needles and injections as being the most negative event to happen to them in the hospital (Doughty, 1959). In addition, rectal administration of midazolam may be an uncomfortable and embarrassing procedure for children, and may also be distressing to parents (McCluskey & Meakin, 1994). Finally, nasal administration may produce a burning sensation that is upsetting to children (McCluskey & Meakin, 1994). As noted by Weldon, Watcha, and White (1992) the oral route of medication remains the least threatening administration method. When midazolam was introduced in oral form, researchers suggested that it might be more useful as a pre-operative medicant than existing forms administered via other routes. Studies of oral midazolam solution (10 mg) indicate that the time of peak

plasma concentration after administration is approximately 22 minutes, with most patients being asleep or extremely drowsy within 30 minutes (Smith, Eadie, & O'Rourke-Brophy, 1981). Midazolam has a short-half life (approximately 2 hours) which makes it very useful in a day surgery setting, because patients are not likely to be under the effects of the drug by the time they leave the hospital (Smith et al., 1981). In fact, the half-life of midazolam is most likely shorter in children than it is in adults, perhaps due to faster metabolism (Salonen, Kanto, Iisalo, & Himberg, 1987).

O'Boyle, Barry, Fox, Harris, and McCreary (1987) investigated the usefulness of oral midazolam (15 mg) as a pre-operative medicant in an adult, dental population. Unfortunately, no placebo group was used in this study. Prior to the administration of midazolam, participants were shown 6 pictures. Three of the pictures were of neutral items (e.g., a teaspoon), while three were pictures of dental items (e.g., dental tools). Again, at 40 minutes post-drug, participants were shown another series of 6 pictures of neutral and dental items. At both encoding periods, participants were asked to name each picture to ensure that the pictures were adequately encoded. One week after the surgery, participants were given a recognition task (12 new and 12 previously-encoded pictures). In addition, participants were given a list of surgery events (e.g., mouth injection, drilling) and were asked to indicate if they remembered each event "perfectly", "vaguely" or "not at all". The results indicated that the participants showed very little amnesia for pictures shown before midazolam, as compared to marked amnesia for the stimuli presented 40 minutes after midazolam administration, with average memory of 5.5/6 pictures and 1.7/6 pictures, respectively. Before drug administration, there was no difference in the participant's memory for dental and neutral stimuli. However, at the

post-drug testing time there was a marginal difference between memory for neutral and dental pictures ($p < .08$), with the midazolam-treated participants remembering more dental pictures than neutral pictures. In addition, more than 40% of participants reported vague or no memory for injections and drilling. Certainly, these results lend support to the idea that oral midazolam produces anterograde amnesia on explicit memory tasks. However, without a comparative placebo group, specific conclusions are not warranted.

Overall, few placebo-controlled studies have been conducted which have investigated the use of oral midazolam as a pre-operative medicant in a paediatric surgery situation. All studies which have investigated the sedative effects of oral midazolam in children have found increased observer-rated sedation (using drug group blind observers) in midazolam-treated participants (using doses of .50 or .75 mg/kg), as compared to both pre-midazolam sedation levels, and the sedation levels of placebo-treated participants (e.g., Feld, Negus, & White, 1990; Weldon, Watcha, & White, 1992). Significant sedation has been noted at both 15 minutes (pre-theoretical peak) and 30 minutes (post-theoretical peak) after midazolam administration, with higher levels of sedation being observed at the 30-minute time-point (Weldon et al., 1992). Unfortunately, only observer-rated sedation measures have been used to measure the effects of oral midazolam in children. As noted in Chapter 1, it is important that objective sedation measures are also used, as participants who appear sedated to an observer may not actually show decreased performance on an objective sedation (e.g., psychomotor speed) task.

Overall, most studies of midazolam as a pre-operative medicant in paediatric surgery populations have found decreased observer-rated anxiety in midazolam-treated

participants, as compared to placebo-treated participants. This difference has been observed at the time of anaesthetic administration (Cray, Dixon, Heard, & Selsby, 1996; Feld et al., 1990; Kain, Mayes, Wang & Hofstadter, 1999; McCluskey & Meakin, 1994; Weldon et al., 1992) and upon entry to the operating room (Kain et al., 1999). In each of the above studies, anaesthetic administration occurred at the time of peak (Cray et al., 1996 – 30 min.; Weldon et al., 1992 – 20 min.) or post-peak (McCluskey & Meakin, 1994 – 30-60 min.) plasma levels of midazolam. However, when Cray et al. (1996) re-analyzed their results after dividing their participants into two age groups, only midazolam-treated (.75 mg/kg) children aged 6 and below had anxiety levels that were significantly different from placebo-treated children. It is possible that these results are due to lower overall anxiety levels in older children, leading to a “floor effect”.

The effect of oral midazolam on memory has rarely been studied in a paediatric surgery population. Feld et al. (1990) showed children one picture at approximately 40 minutes post-midazolam (.75 mg/kg). Immediately before leaving the hospital children were asked to recall (free recall or cued recall) the picture that had been shown to them. Midazolam-treated participants were less likely to recall the picture than placebo controls, indicating impaired explicit memory. Also, fewer midazolam-treated, than placebo-treated, children recalled the application of the mask, indicating an amnesic effect of the drug on a perhaps more ecologically valid measure of explicit/episodic memory (i.e., memory for a real life personal experience). In another study, participants received oral midazolam (.40-.60 mg/kg) (combined with atropine) approximately one hour before surgery (Saarnivaara, Lindgren, & Klemola, 1988). Unfortunately, no placebo group was used in this study. Immediately before the administration of

anaesthesia, the children were shown two pictures and asked to name them. Two hours after the operation they were asked to recall the pictures in a free recall task. The results indicated that more than 80% of children remembered the pictures shown to them before surgery, failing to provide any strong support for midazolam-induced disruptions in explicit memory performance. However, encoding took place one hour after administration of midazolam, which is well after the time of theoretical peak plasma concentrations of the drug. Thus, the effects of the drug were likely to be dissipating by the time of encoding. In addition, it is not possible to determine what percentage of placebo participants would have had memory for the pictures to evaluate whether the 80% correct recall does in fact represent a reduction in explicit memory abilities induced by midazolam.

As it appears that oral midazolam reduces anxiety in the hospital setting, and some evidence suggests that the drug impairs memory, researchers have hypothesized that midazolam-treated participants will show fewer behavioural problems upon returning home after surgery. Studies indicate that behaviour problems in the first few weeks following surgery, as rated by parents, are less common in midazolam-treated children, as opposed to children who received a placebo (Kain et al., 1999; McCluskey & Meakin, 1994). The most frequently reported post-surgery behaviour changes were temper tantrums, eating disturbances, anxiety, and nightmares. In addition, parents in the Kain et al. (1999) study were not informed of their child's drug group (placebo or midazolam [.50 mg/kg]) status before completing the questionnaire about post-surgery behaviour. McCluskey and Meakin (1994) did not indicate if parents remained blind to their child's drug group status when completing the post-operative questionnaire. Kain et al. (1999)

suggested that these findings of less post-surgery disturbance in midazolam-treated children might be mediated by midazolam-induced amnesia for the surgery experience. However, they did not directly test this hypothesis.

A recent survey of premedication practices in the United States (Kain et al., 1997) indicates that midazolam is, by far, the most commonly used premedicant in paediatric surgery settings. The results of the survey also indicated that the use of premedication in the United States is quite variable, with between 10-75% of children being routinely premedicated, depending on the geographic location surveyed. Although results are not available for Canada, Kain and associates (1997) reported that pre-medication in paediatric settings is less common in Great Britain. Reasons cited for not using midazolam as a premedicant include concerns about safety and prolonged recovery due to sedation (Sandler et al., 1992).

Researchers have investigated the possibility that midazolam-treated participants will spend a longer time in the recovery room, due to the sedative effects of the drug (Sandler et al., 1992). Certainly, in a busy day surgery setting, prolonged stays in the recovery room could be a significant problem, and could create a bottleneck effect. Currently, there is little consensus in the research literature regarding the effects of oral midazolam on length of recovery-room stays. Weldon et al. (1992) found that recovery from anaesthesia was not prolonged in the midazolam group (.50 mg/kg), as compared to the placebo group. Another study (Parnis, Foate, VanDerWalt, Short, & Crowe, 1992) found a significant difference in the time spent in the recovery room after oral midazolam (.50 mg/kg), although the researchers suggested that the average 6-minute time extension in midazolam vs. placebo treated children was not a clinically relevant difference.

Similarly, another study found that midazolam-treated (.50 mg/kg) participants stayed in the recovery room an average of 7 minutes longer than placebo-treated participants (McCluskey & Meakin, 1994). However, another study found that midazolam-treated (.75 mg/kg) participants took 11-minutes longer to wake and remained in the recovery room for 30 minutes longer than placebo-treated participants (Cray et al., 1996). With only one exception, these studies converge in suggesting that midazolam results in increased time in the recovery room post-surgery. However, the studies differ markedly in their findings regarding the precise amount of time increase involved. In addition to the different doses of midazolam given in the above studies, it is likely that the variations in the above studies are a result of midazolam being given at different time-points before surgery, and comparison of surgeries with variable lengths. Hypothetically, if the effects of midazolam wear off within two hours, recovery may be prolonged after a 10-minute surgery (depending on when the drug is given pre-surgery), but should not affect length of recovery after a long surgery. Therefore, in studies that examine the effects of midazolam on recovery time, two variables should be comparable in the placebo and midazolam groups: the time the drug was given before surgery, and the actual length of the surgery. In each of the above studies, surgeries/medical procedures with various lengths were used within the same study. In addition, some of the studies did not adequately control for the time that midazolam was given before surgery (McCluskey & Meakin, 1994; Parnis et al., 1992).

As noted by Kain, Mayes, Wang, Caramico, and Hofstdter (1998), another reason cited for not using midazolam premedication is the belief that parental presence in the operating room will reduce anxiety, making premedication unnecessary. Kain and

associates (1998) investigated this hypothesis by comparing three groups of children having day surgery. One group of children received oral midazolam (.50 mg/kg) at least 20 minutes before the surgery. One group of children had their parents accompany them to the operating room and stay throughout the anaesthetic induction. The final group of children was a control group who did not receive medication or have parental accompaniment to the operating room. The results indicated that the midazolam group was rated by observers as being significantly less anxious than both the placebo-treated participants and the parental accompaniment group when entering the operating room and when the mask was placed on the face. The percentage of anaesthetic inductions that were rated as "poor" was higher in the control group, as compared to both the other two groups. In addition, it should be noted that almost half of parents have extremely high levels of anxiety before a child's surgery (Thompson, Irwin, Gunawardene, & Chan, 1996) and this anxiety can lead to increased child anxiety (Bevan et al., 1990) possibly explaining the lack of overall anxiolytic effect of parental presence relative to controls in the Kain et al. (1998) study.

Overall, the above studies indicate that oral midazolam is an effective anxiolytic and sedative drug, when used as a premedicant in paediatric surgery populations. Unfortunately, very little research has been conducted on the effects of oral midazolam on implicit and explicit memory in this population. In addition, there are many apparent problems with the tasks that have been used to assess memory in the studies to date. A comparison of the quality of memory tasks used in the anaesthesia literature and psychopharmacology journals indicated that anaesthesia studies are less likely to use formal, validated memory assessment techniques (Ghoneim, Ali, & Block, 1990). The

most common memory tasks used in the anaesthesia literature are small numbers of pictures that are tested with a free recall or recognition task, or specific questions regarding memory for surgery events. Studies in the anaesthesiology literature are less likely to use a placebo group, to measure memory at both pre- and post-treatment (to ensure equivalence of groups prior to drug administration), and to use memory tests based on a theoretical model of memory (Ghoneim et al., 1990). Certainly, well-designed studies of the memory effects associated with oral midazolam in a paediatric surgery population have yet to be conducted, with no previous attempt to study priming. However, it should be noted that a few studies in the adult literature, conducted without knowledge of the possible time-dependent effects of BZs, indicate that implicit memory is impaired by midazolam (DeRoode et al., 1995; Ghoneim et al., 1993). Even though these researchers were not concerned about the time-dependent effects of BZs, due to the fast absorption rate of midazolam it is likely that plasma drug concentrations would have been near theoretical peak by the time the encoding stimuli were presented in these previous studies. Moreover, it is unlikely that memory encoding would have occurred at post-peak testing times, as most participants would have been too sedated to test after 20 minutes post-drug administration (Smith et al., 1981).

In a pilot test for the third study in this thesis, both implicit and explicit memory were tested in 10 children outside a hospital context, to ensure that the chosen tasks adequately measured memory processes in 4 to 6 year old non-medicated children. Eight children were pilot tested in their homes and two children were tested in a university laboratory setting, all in the presence of their mothers. Children were tested with the

same variation of the Greenbaum and Graf (1989) implicit and explicit memory tasks that were used with the patient participants in Study 3 (see below).

Study 3 was designed to determine the time course of midazolam's effects on explicit and implicit memory in a placebo-controlled design when the drug was used as a premedicant for 4-6 year old children having ear tube (myringotomy) surgery. The amnesic effects of the drug were tested at two Encoding Times: before the peak blood concentration of midazolam (5 minutes post-drug administration) and close to the theoretical peak blood concentration of midazolam (20 minutes post-drug administration) (Smith et al., 1981). An independent-groups design was used, where children only encoded the memory stimuli at one of the two Encoding Times, to reduce the likelihood of explicit contamination of the implicit memory task due to repeated memory testing (Legrand et al., 1995). The implicit and explicit memory tasks were actually administered to each child at two time periods. The first testing time, similar to the testing time in Studies 1 and 2, occurred soon after the encoding task (at either 5 or 20 minutes post-drug). Therefore, children would still be directly under the influence of midazolam while the memory testing was being conducted. The second testing time occurred after the surgery was completed (approximately 130 minutes after drug administration). At this time, it was expected that children would no longer be directly under the influence of midazolam. Therefore, if memory remained impaired at the second testing time, it would indicate a BZ-induced encoding or storage difficulty, as opposed to a difficulty with retrieval while under the influence of midazolam. The present study used an explicit memory test and an implicit test which satisfied the retrieval intentionality criterion

(Schacter et al., 1989), and which used child-normed stimuli (cf., Greenbaum & Graf, 1989).

In addition to the explicit task above, a second explicit task was administered which was designed to be a more ecologically-valid, real-world memory task. In this task, children were asked for their free recall of events that happened to them on the day of the surgery. Children's memories for events occurring when they were and were not under the influence of the drug were compared. This task was administered both on the day of the surgery and again at the child's follow-up appointment.

The present study also attempted to extend knowledge about the additional cognitive effects of midazolam. First, the attentional effects of midazolam premedication have never been studied, and the present study included a task assessing focused attention that has been specifically designed for use with children (Corkum, Byrne, & Ellsworth, 1995). In addition, both observer-rated and objective sedation were assessed to determine the extent of the sedative effects of midazolam. Finally, the clinical relevance of midazolam was assessed by examining children's anxiety during administration of anaesthetic and their acceptance of the mask, the time taken to recover after surgery, problems and behaviour upon waking, and parent-ratings of children's post-hospital behavior in the weeks following the surgery.

Based on previous research with BZs (e.g., Study 1 and Study 2), it was predicted that at the pre-peak testing time (5 minutes post-drug), midazolam would impair explicit memory (free and cued recall), while leaving priming intact. However, at the peak testing time (20 minutes post-drug), it was predicted that both explicit and implicit memory would be impaired. In addition, it was hypothesized that sedation (objective and

subjective) and attention would be impaired by midazolam at both time-points. Also, based on previous research on oral midazolam (Cray, et al., 1996; Feld et al., 1990; Kain et al., 1999; McCluskey & Meakin, 1994) it was predicted that midazolam-treated participants, as compared to placebo-treated participants, would show decreased anxiety during administration of anaesthetic. In addition, it was hypothesized that the midazolam-treated participants would have a longer recovery time after the relatively short myringotomy surgery. It was also predicted that midazolam children would be calmer when waking after surgery, compared with placebo children. Finally, it was hypothesized that midazolam-treated children would show fewer parent-rated behavioural problems in the week following the surgery.

Materials and Methods

Participants

Pilot Participants. Ten children were pilot tested in their homes or in a university laboratory setting. The pilot participants were healthy 4-6 year old children (mean age = 5 years, 4 months, SD = 10.68 months). Gender distribution was 5 males and 5 females.

Study Participants. Participants in the present study were forty 4-6 year old children (mean age = 5 years, 5 months, SD = 10.32 months) who were scheduled for ear tube insertion (myringotomy) at the IWK Grace Health Centre (IWK Grace). Aside from their need for ear tube insertion, participants were otherwise healthy. Gender distribution was twenty-four boys and sixteen girls (3:2 ratio of boys to girls). To avoid potential confounding variables, any history of neurological or cognitive impairment or disease, as reported by parents, excluded myringotomy surgery recipients from participation in this study. Specifically, one child with Downs Syndrome and another with severe mental

retardation were excluded from participation. Children with a previous adverse reaction to BZs or Tylenol™ as reported by parents were also excluded from the study, as were children who were taking medication other than antibiotics at the time of the study. Participants were instructed to refrain from eating after midnight the night before the study as per normal pre-surgery hospital procedure. Parents of each participant provided written informed consent before participation. In addition, each child provided verbal assent. This study had IWK Grace Ethics Review Board approval.

Only children undergoing purely myringotomy surgery (i.e., not in conjunction with other surgeries) were used in the present study because the procedure and anesthetic are simple and easily standardized. The age group of 4-6 years was chosen for several reasons. First, preschool children are most likely to require ear tubes (Giebink & Daly, 1990). Secondly, based on a review of the literature (see Chapter 5), children under 4 years of age were excluded due to the difficulty of designing implicit and explicit memory tasks for very young children. Finally, children over 6 years of age were excluded because of developmental improvement in explicit memory performance (see Chapter 5).

Experimental Design and Drugs. The present study used a randomized, placebo-controlled design. Participants were randomly assigned to one of four groups, with ten participants per group. The two midazolam groups received a mixture of Children's Tylenol™ suspension and oral midazolam and the two placebo groups received only Children's Tylenol™. Acetaminophen (the active ingredient in Children's Tylenol™) is given routinely to children at the IWK Grace before myringotomy. Midazolam (Versed™ [Roche] for intravenous administration, 5 mg/ml) at a dose of 0.50 mg/kg was mixed with

acetaminophen (Tylenol™ [McNeil Consumer Products, Canada, Inc.] grape-flavored suspension, 32 mg/ml) at a dose of 15 mg/kg. The placebo group received only the Tylenol™, without the addition of midazolam. Drug administration was double-blind in that the child, his/her parents, and the researcher who was testing the child were not aware of the child's group placement. Only the nurse responsible for administering the drug was aware of the child's group assignment. Nurses had no involvement in the cognitive testing of the child participants. In case of problems or emergency, nurses or doctors could discover the child's drug group status by opening an envelope contained in the child's file. Within the midazolam and placebo groups, participants were randomly assigned to 5 minute or 20 minute testing times. This assignment was not double-blind, as it was not possible to keep participants or experimenters blind to the time between drug administration and the encoding task.

Tasks and Procedure. When a 4-6 year old child was scheduled for myringotomy surgery at the IWK Grace, an information package was sent to the child's parents that informed them of the study details. Parents were informed that we were attempting to determine if a drug that was sometimes given before surgery is effective in reducing children's anxiety and whether it affects children's memory for events prior to surgery. Parents were also informed that their surgeon was aware of the study. One week after the letter was mailed to the parents, the parents were contacted by phone. Parents were verbally informed of the study purposes and procedures, and any parental questions were answered. If parents provided verbal consent for their child to participate in the study, they were asked several questions to ensure that no exclusionary criteria (see above) were met.

On the day of the surgery, approximately 90 minutes prior to surgery, the researcher met with both the child and the parent(s) to obtain parental written informed consent and child verbal assent for the child's participation in the study. Once consent/assent had been obtained, the child's baseline level of sedation was rated by the experimenter using a 5-point rating scale (Wilton et al., 1988). The anchors (and associated descriptors) on this scale were as follows: 1 = agitated (clinging to parent and/or crying), 2 = alert (awake but not clinging to parent, may whimper but not crying), 3 = calm (sitting or lying comfortably with eyes spontaneously open), 4 = drowsy (sitting or lying comfortably with eyes spontaneously closing but responds to minor stimulation), and 5 = asleep (eyes closed, rousable but does not respond to minor stimulation) (Wilton et al., 1988). This observer-rated sedation measure was chosen for use in the present study because it has been used previously in studies of midazolam as a preoperative medicant in children (i.e., Wilton et al., 1988). However, its psychometric properties remain unknown. Children's anxiety level was also rated by the experimenter using the Modified Yale Preoperative Anxiety Scale (mYPAS; [Appendix Q]; Kain et al., 1995). This observational instrument of anxiety contains 27 items in five categories of anxious behaviors characteristic of young children (i.e., activity, vocalization, emotional expressivity, state of apparent arousal, and use of parents). Each of the five categories of anxious behavior is rated on scales ranging from 1-4 (except vocalizations, which is rated on a 1-6 scale). No scorable rating is provided if the observer is uncertain or if the child is not visible at the time of the rating. Total scores can range from 5 to 22 with higher scores reflecting greater levels of anxiety. The mYPAS has good to excellent inter-observer and intra-observer reliability and demonstrated validity for measuring paediatric

anxiety during the induction of anaesthesia (Kain et al., 1997). Specifically, the mYPAS total score shows good concurrent validity with the State Trait Anxiety Inventory for Children (Spielberger, 1973) and good construct validity in that total mYPAS scores increase with stress induction in the surgery context (Kain et al., 1997). Only the total mYPAS score was used in the present study.

Next, the child and parent(s) were escorted to the day surgery area and met with the nurse assigned to the child. The nurse weighed the child and obtained other necessary information typically required in the pre-surgery context. This weight information was also used in determining dose of drug administered in the present study (i.e., in mg/kg). In addition, an anaesthesiologist met with the child to perform a pre-anesthetic assessment, to ensure medical eligibility for the study, and to order the study medications (this was not the same anaesthesiologist who administered anaesthetic to the child during surgery).

Before the study drug (midazolam or placebo) was administered, children were given a variety of cognitive tasks to ensure pre-drug equivalence between groups. First, the child was given the Narrative Memory Task from the NEPSY ([Appendix R]; Korkman, Kirk, & Kemp, 1997), to ensure pre-drug equivalence in memory performance. In this task, the child is told a short story and immediately tested for free recall and cued recall of the story information (cued recall and free recall are combined to create a total memory score). In addition, children were administered the Picture Deletion Task for Preschoolers (PDTP; [Appendix S]; Corkum, Byrne, & Ellsworth, 1995) to ensure pre-drug equivalence in attentional performance. In this task, after a few practice items, children are presented with a page of 60 shapes and asked to scan the page to find all

examples of a specific target shape (10 diamonds or triangles). Children use a bingo marker to mark each target shape. Time taken to complete the task, as well as omission and commission errors were measured. Next children were given the Motor Deletion Task (MDT; [Appendix T]; Corkum et al., 1995), to ensure pre-drug equivalence in objective sedation. In this task, they were presented with a page of 60 circles and asked to put a mark in each circle on the page as quickly as possible, with a maximum time limit of five minutes. Time to complete this psychomotor speed task was used as the measure of objective sedation. If a child was not finished this task by the time the five-minute limit had elapsed, he/she received a score of five minutes independent of how many targets had been marked. After these baseline cognitive measures were completed, at approximately 50 minutes before surgery, the participants received either the midazolam/Tylenol mixture or Tylenol alone (placebo).

At the appropriate testing time (5 or 20 minutes post-drug administration) participants were shown a series of 12 line drawings [see example in Appendix U] and asked to identify each of them. Intentional learning instructions were used, with children being told that they were going to be asked about the pictures at a later time. Following Greenbaum and Graf (1989), the materials were 27 line drawings of common objects. Although we were unable to obtain the original stimulus materials used by Greenbaum and Graf (1989), we used pictures of the same items as those described in their original study. Additionally, except where noted, all task procedures were identical to those used by Greenbaum and Graf (1989). Specifically, twenty-four pictures were used to form four sets of six targets and three cards were used as practice items. Each picture was shown on a 10x15 cm index card. The six items in each set were all from the same

category (kitchen, zoo, park or restaurant). Each child saw pictures from 2 of the 4 categories (12 pictures): park and restaurant or zoo and kitchen. Which set of stimulus materials a particular child encoded was counterbalanced across the four study groups. During encoding, children were shown each picture for 3 seconds. If the child could not identify the picture, or misidentified the picture, he/she was informed of the correct picture name and asked to repeat it [Appendix V].

After the encoding task, sedation and anxiety were again rated by the experimenter using the 5-point rating scale and the mYPAS, respectively. Next, the children were again given the PDTP (using the target shape [diamond or triangle] that was not presented pre-drug) and the MDT. Children were then administered the implicit memory task from the Greenbaum and Graf (1989) study [Appendix W]. In this task, children were told a short story which described a scenario in which a child of the same gender and age as the participant goes to a particular place (i.e., kitchen, zoo, park, or restaurant). Each story ended with the following question “What do you think [child’s name] saw at/in the [place]? Tell me everything you think he/she might have seen.” The category (i.e., kitchen, zoo, park, or restaurant) used in this first story was one of the two categories that the child had not encoded during the picture naming (encoding) task (i.e., unprimed condition). The child was then told a second story, involving one of the categories that they had encoded during the picture naming (encoding) task (i.e., primed condition). Thus, on the implicit memory task, the unprimed (baseline) condition always preceded the primed (experimental) condition, for consistency with the procedures of Greenbaum and Graf (1989). The implicit memory task was followed by an explicit memory task in which children were “cued” with the back of the picture cards and asked

to list the pictures they saw from a specific category (e.g., "Can you name the pictures I showed you of things you see in a restaurant.") (Appendix X). Which word sets were used in the unprimed implicit, primed implicit, and explicit tasks depended on which had been presented in the initial encoding as well as a pre-determined counter-balancing of order across study groups. For example, a child who encoded park and restaurant during the picture-naming task might receive zoo as the unprimed category and restaurant as the primed category in the implicit task, and park as the cued category in the explicit task. Alternatively, he/she might receive kitchen as the unprimed category and park as the primed category in the implicit task, and restaurant as the cued category in the explicit task. The memory tasks were terminated when the child indicated that he/she could not name any more objects (cf. Greenbaum & Graf, 1989).

When the child had finished the memory tasks, he/she was taken to the surgery room. All children separated from their parents when leaving the day surgery room, as per typical IWK Grace procedure. For all study participants, anaesthesia was induced using only halothane/nitrous oxide (N₂O) via a mask. The experimenter again rated the child's level of anxiety during the administration of anaesthesia using the mYPAS. In addition, the child's acceptance of the mask was rated by the experimenter on a three-point Likert scale with anchors of "calm", "frightened", and "hysterical".

Time taken to wake in the recovery room was measured (i.e., time from drug administration to child opening eyes and being responsive, in minutes). In addition, the recovery room nurses, who were unaware of the child's Drug Group status, rated the child's awakening as "smooth", "restless" or "stormy". Although no reliability data exist for these latter nurse ratings, they are common procedure at the IWK Grace. Need for

pain medication (e.g., Codeine, Tylenol™) was noted. In addition, any problems (e.g., nausea, vomiting, crying) after waking were noted. Time taken for the child to leave the recovery room was also measured (i.e., time from drug administration until child was returned to Day Surgery room, in minutes).

After the child was awake and returned to the Day Surgery room, he/she was given the implicit and explicit memory tasks a second time. During this administration, the implicit task used the primed items that were used in the previous explicit task and vice versa. For example, a child who encoded park and restaurant during the picture naming task, and who received park as the cued category in the first explicit task, kitchen as the unprimed category and restaurant as the primed category would receive park as the primed category and zoo as the unprimed category in the second implicit task and restaurant as the cued category in the second explicit task. This method of counterbalancing was used to control for within-category practice effects on the explicit memory task. Finally, the child was asked for his/her free recall of the events that had happened to him/her since arriving at the hospital (i.e., “Can you tell me about what happened today since you came to the hospital?”). The experimenter recorded each of the participants’ answers verbatim (Appendix Y).

At the child’s follow-up appointment with the surgeon, which occurred approximately six weeks after the child’s surgery, parents were asked to complete the Post Hospitalization Behavior Questionnaire (PHBQ; [Appendix Z]; Vernon, Schulman, & Foley, 1966) to assess any changes in the child’s behavior within the first week after the surgery. This is a 27-item questionnaire that is widely-used in the surgery literature, and is designed to evaluate maladaptive behavioural responses and “behavioural

regression" (i.e., loss of previously gained developmental milestones such as losing bladder control or losing previously gained language abilities) in children after surgery (Kain et al., 1999). The measure shows good psychometric properties such as good agreement with psychiatric interviews of parents of preschoolers (Vernon, Schulman, & Foley, 1966). Factor analysis indicates that the scale can be broken down into six subscales (General Anxiety and Regression; Separation Anxiety; Anxiety About Sleep; Eating Disturbance; Aggression Toward Authority, and Apathy-Withdrawal) (Vernon et al., 1966). Next, each child was again asked for his/her memory (free recall) of the events that had taken place on the day of the surgery ("Can you tell me what happened a few months ago when you went to the hospital?"). The experimenter again recorded each of the participants' answers verbatim.

Results

Statistical Analysis. Drug Group effects were examined with separate ANOVAs, Chi-Squares, t-tests or ANCOVAs with the aid of the SPSS for Windows statistical software package (SPSS Inc., 1998). The majority of the data was analyzed with a series of 2 x 2 (Drug Group x Encoding Time) ANOVAs. However, due to my a priori predictions of time course effects on memory performance on the Greenbaum and Graf (1989) task, and to maintain consistency with Study 2 data analytic procedures, separate one-way (Drug Group) ANOVAs were conducted on the cued recall and priming tasks at each Encoding Time. In contrast, the free recall and recovery data were analyzed with one-way (Drug Group) ANOVAs or t-tests after collapsing across levels of the Encoding Time factor because no effects of time course were theoretically expected here. The time taken to complete the objective sedation task and the attentional measures were analyzed with a

set of 2x2x2 ANOVAs (Drug Group x Encoding Time x Drug Phase [pre- vs. post-drug]) with repeated measures. The anxiety measure was analyzed with a 2 x 3 (Drug Group x Drug Phase [pre-drug vs. post-drug vs. anaesthetic administration]). All categorical data was analyzed with Chi-Square analysis.

Pilot Testing. Pilot testing of the Greenbaum and Graf (1989) implicit and explicit tasks was conducted to ensure that the tasks were adequate measures of memory in 4-6 year old children. On the cued recall task, the pilot participants correctly remembered an average of 2.1 target pictures ($SD = 1.20$) indicating some level of explicit memory (memory for approximately 1/3 of the target pictures). Despite our slight change to the Greenbaum and Graf (1989) procedure for assessing explicit memory (i.e., that we modified the task to satisfy the retrieval intentionality criterion), our findings were fairly consistent with those of Greenbaum and Graf in which 4 year old children remembered an average of 1.9 pictures and 5 year old children remembered 2.8 pictures. Six year old children were not used in the Greenbaum and Graf (1989) study. On the priming task, the pilot participants named an average of 2.8 primed pictures, as opposed to 0.5 unprimed pictures. A one-way within-subjects ANOVA indicated a significant effect of priming, with more primed than unprimed words being correctly completed by pilot participants ($F(1,9) = 78.05, p < .0001$). This indicates that the implicit memory task is an adequate measure of priming in 4-6 year old children. These findings are fairly consistent with Greenbaum and Graf (1989) in which children correctly named an average of 1.4 (4 year olds) and 1.8 (5 year olds) primed pictures as compared to an average of 0.8 unprimed pictures (both age groups combined).

Study Participants

Participant Characteristics. A series of four-group (midazolam pre-peak, midazolam peak, placebo pre-peak, and placebo peak) Chi-Square analyses were conducted to determine if the groups differed on any of the categorical control variables. There was no effect of Group for the number of children taking medication, the number of females or the number of children who had previously had surgery. Only one child had previously taken midazolam, so this variable was not analyzed statistically. In addition, a 2 x 2 (Drug Group x Encoding Time) ANOVA indicated that the four groups did not differ significantly in age. Descriptive statistics for these control variables are illustrated in Table 7 as a function of Drug Group and Encoding Time.

Pre-Drug Cognitive Functioning. Pre-drug measures of narrative memory (total memory score from NEPSY), objective sedation (time to complete MDT in seconds), and attention (time to complete PDTP, as well as number of omission and commission errors) were analyzed with a series of 2 x 2 (Drug Group x Encoding Time) ANOVAs to determine if the four groups were equivalent prior to the drug administration. As children demonstrated both omission and commission errors, a combined attention score was not created. This is because omission and commission errors are likely measuring different attentional processes (Aman & Turbott, 1986), and combining them might make it difficult to interpret a Drug Group effect. There were no significant effects of Drug Group or Encoding Time on any of the pre-drug cognitive measures. In addition, on the observer-rated sedation measure, all 40 children were rated by the experimenter as "calm" (i.e., mid-point of "3" on the 5-point Likert scale; Wilton et al., 1988) before being administered the drug. On the observer-rated anxiety measure (mYPAS), all

children received scorable ratings (“uncertain” and “can’t see child” were never coded). The child's score on the Use of Parent scale on the mYPAS was subtracted from the total score create an anxiety score which could be directly compared to the child's score during anaesthetic induction (when parents were not present). There were no pre-drug group differences on these modified mYPAS scores. Means and SDs for these pre-drug cognitive and observer-rated measures are displayed in Table 8 as functions of Drug Group and Encoding Time.

Table 7
Descriptive Statistics on the Control Measures as Functions of Drug Group and Encoding Time.

	Drug Group			
	Placebo		Midazolam	
Encoding Time (min. post-drug administration)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)
Mean and (SD):				
Age -in months	64.10 (11.75)	66.40 (12.51)	64.70 (7.56)	66.90 (10.18)
Frequencies:				
Previous Use of Midazolam	0	0	1	0
Taking Medication	3	2	3	0
Previous Surgery	6	4	8	7
Sex (# of females)	4	5	2	5

Table 8
Means (and SDs) on the Pre-Drug Measures of Cognitive Functioning, as Functions of Drug Group and Encoding Time.

	Drug Group			
	Placebo		Midazolam	
Encoding Time (min. post-drug administration)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)
Memory - NEPSY - Number of story items remembered	9.50 (4.88)	11.70 (6.38)	9.80 (5.43)	11.90 (5.34)
Objective Sedation - Time (sec.) to complete MDT	52.40 (20.54)	58.70 (22.75)	61.00 (26.02)	53.10 (17.22)
Attention Speed - Time (sec.) to complete PDTP	45.40 (17.31)	44.10 (13.30)	43.80 (16.92)	50.60 (17.38)
Attentional Omissions - Number of omissions on PDTP	0.60 (1.58)	0.70 (1.57)	1.10 (1.52)	0.20 (0.63)
Attentional Commissions - Number of commission errors on PDTP	0.50 (1.58)	0.10 (0.32)	1.40 (3.44)	0.00 (0.00)
Experimenter-Rated Anxiety - Child's score on the mYPAS	5.60 (2.01)	4.80 (1.03)	4.70 (1.57)	4.60 (0.84)

Memory, NEPSY Narrative Memory Task (Korkman et al., 1996); MDT, Motor Deletion Task (Corkum et al., 1995); PDTP, Picture Deletion Task for Preschoolers (Corkum et al., 1995), mYPAS (revised total – omitted Use of Parents scale), Modified Yale Preoperative Anxiety Scale (Kain et al., 1995).

Memory Effects

Explicit Memory

Free Recall. To analyze the participants' free recall of the events that had happened to them in the hospital, possible hospital events were broken down into 15 categories (e.g. getting registered, going to the operating room) by my own initial drug-group-blind review of the types of responses produced by the children on this task (Appendix AA). Children's responses were then scored for the number of categories contained in their responses (child scores a one for each category named, but each category is only scored once). For example, a child naming three distinct events occurring during the cognitive testing phase (e.g., use of bingo marker, memory for a story, searching for triangles) scored a one for all three responses because "Cognitive Tasks" was deemed a single category. Next, the 15 categories were further broken down into ten sub-categories containing events that likely occurred when the child was not under the influence of the drug (e.g., Nursing Tasks) and five sub-categories of events that most likely occurred when the child was under the influence of the drug (e.g., Getting Anaesthetic). To ensure reliable scoring, a second individual, also without knowledge of participants' Drug Group status, again independently scored these two free recall sub-categories for all participants. The inter-rater reliability coefficient (Hartman, 1977) was 1.00 for both occurrences under drug/placebo influence and occurrences not under drug/placebo influence at the post-surgery testing time, indicating perfect agreement. At the follow-up appointment, the reliability coefficient was again a perfect 1.00 for occurrences not under drug/placebo influence and a high 0.93 for occurrences that occurred under the influence of

midazolam/placebo, indicating excellent inter-rater reliability. As inter-rater differences were rare, I always relied on my response for final scoring when a discrepancy occurred.

As there is no theoretical reason to expect Encoding Time differences in the number of events recalled on this free recall measure either while non-drugged or under the influence of midazolam/placebo, the free recall data was collapsed across Encoding Time. On the day of the surgery, a one-way (Drug Group) ANOVA revealed no significant main effect of Drug Group ($F(1, 38) = .43, n.s.$) for the number of occurrences remembered for events likely occurring when participants were not under the influence of the drug/placebo. However, the midazolam-treated participants remembered fewer occurrences of events that likely occurred when they were under the influence of the drug when compared with the placebo-treated participants ($F(1,38) = 4.97, p < .05$). Means and SDs for “under the influence” and “not under the influence” free recall are displayed in Table 9 as a functions of Drug Group.

At the follow-up appointment, a one-way (Drug Group) ANOVA again revealed no significant effect of Drug Group ($F(1, 38) = 2.50, n.s.$) for the number of pre-drug occurrences remembered. For the free recall of events likely occurring while children were under the influence of drug/placebo, there was a marginally-significant effect of Drug Group ($F(1, 38) = 2.80, p = .10$), with midazolam-treated participants again tending to recall fewer events than placebo controls (see Table 9). Table 9 shows that the dissipation of the Drug Group effect on memory for events occurring while under drug influence from the day of the surgery to the follow up appears to have been due to a slight decay in memory for these events in the placebo group over time.

Table 9
Means (and SDs) on the Free Recall Task, as a Function of Drug Influence and Drug Group.

Drug Influence	Drug Group			
	Placebo		Midazolam	
	No Influence	Influence	No Influence	Influence
Day of Surgery	1.50 (1.47)	.66 (.93)	1.20 (1.44)	.15 (.37)
Follow-Up	1.85 (1.60)	.50 (.69)	1.15 (1.14)	.20 (.41)

Cued Recall. Cued recall performance was scored as the total number of target pictures correctly remembered from the encoding task. In the present study, the balanced design permits the use of an omnibus 2 x 2 (Drug Group x Encoding Time) ANOVA. However, to maintain consistency with Study 2 data analytic procedures (different encoding instructions at the three time points in Study 2), separate one-way (Drug Group) ANOVAs were conducted on the cued recall (explicit memory task) scores at each Encoding Time. Explicit memory testing was conducted at two testing periods in a within-subjects design: pre-surgery and post-surgery. Cued recall data from these two testing periods was also examined in separate one-way (Drug Group) ANOVAs due to the potential problems previously noted with the use of repeated memory testing.

Means (and standard errors) for the cued recall task given before surgery (pre-surgery Testing Period), as a function of Drug Group at each Encoding Time, are displayed in Figure 11. As can be seen in Figure 11, the midazolam-treated subjects appeared to recall fewer targets at the peak encoding time, as compared to the pre-peak encoding time whereas no such difference across encoding time is apparent for placebo-treated subjects. At the pre-peak encoding time (5 minute), although means were in the predicted direction with midazolam-treated participants recalling somewhat fewer targets than placebo-treated participants, the pre-peak ANOVA results indicated that there was no statistically significant difference between the midazolam and the placebo-treated participants ($F(1, 19) = 2.13, n.s.$). However, at the peak encoding time, the ANOVA revealed a significant effect of Drug Group, with the midazolam-treated subjects recalling significantly fewer pictures than placebo controls ($F(1, 19) = 15.8, p < .001$) (see Figure 11). Thus, the difference between the cued recall performance of the midazolam and

placebo groups when memory was tested prior to surgery appeared stronger when encoding occurred at peak blood concentrations as opposed to when it occurred at pre-peak blood concentrations (i.e., statistically significant drug effect in the former case but not in the latter case).

Means (and standard errors) for the cued recall task given after surgery (post-surgery Testing Period where midazolam participants would no longer be under the influence of drug) are displayed in Figure 12 as a function of Drug Group at each Encoding Time. As can be seen in Figure 12, once again, the midazolam-treated subjects appeared to recall fewer targets at the peak encoding time, as compared to the pre-peak testing time whereas no such difference across encoding time is apparent for placebo-treated subjects. At the pre-peak encoding time, the results indicated a main effect of Drug Group with the midazolam-treated participants showing impaired cued recall performance, as compared to the placebo group ($F(1, 19) = 5.0, p < .05$). At the peak encoding time, the results again indicated that the midazolam group had impaired cued recall performance, as compared to the placebo group ($F(1, 19) = 10.3, p < .005$). Thus, the difference between the placebo and midazolam-treated participants again appeared somewhat greater when encoding occurred at peak blood concentrations than when it occurred at pre-peak blood concentrations, although the Drug Group effect was statistically significant at both Encoding Times at the post-surgery testing period (see Figure 12).

At both Testing Periods (pre- and post-surgery), and both Encoding Times (pre-peak and peak), the midazolam-treated participants recalled fewer target pictures than the placebo-treated participants (compare Figures 11 and 12). Overall, there was little to no

decay in cued recall performance from the pre-surgery to the post-surgery testing time (compare Figures 11 and 12). There were no differences between the Drug Groups in the total number of answers given (pictures named regardless of accuracy) on the cued recall task at the pre-surgery testing time for either the 5 minute or 20 minute Encoding Time group ($F(1, 18) = .68, n.s.$; $F(1,18) = 1.77, n.s.$). At the post-surgery testing time there was no Drug Group difference in the total number of pictures named for the 5 minute participants ($F(1,18) = .20, n.s.$). However, at the post-surgery testing time there was a marginal Drug Group difference for the 20 minute participants with placebo-treated participants tending to name more pictures overall ($F(1,18) = 4.19, p = .056$). When the number of pictures named was used as a covariate for the 20 minute group at the post-surgery testing time, the Drug Group difference on the Cued Recall task remained significant ($F(1,17) = 5.72, p < .05$). Overall, these results indicate that the differences between the midazolam and placebo treated participants in cued recall performance were not due to a general word retrieval deficit (see means in Table 10); rather they appear to be reflecting a true explicit memory deficit among midazolam-treated children.

Figure 11: Cued Recall Performance: Mean number of pictures correctly recalled on the cued recall test as a function of Drug Group, at each Encoding Time (pre-surgery period). Bars represent standard errors. Asterisk (*) indicates significant difference between Drug Groups.

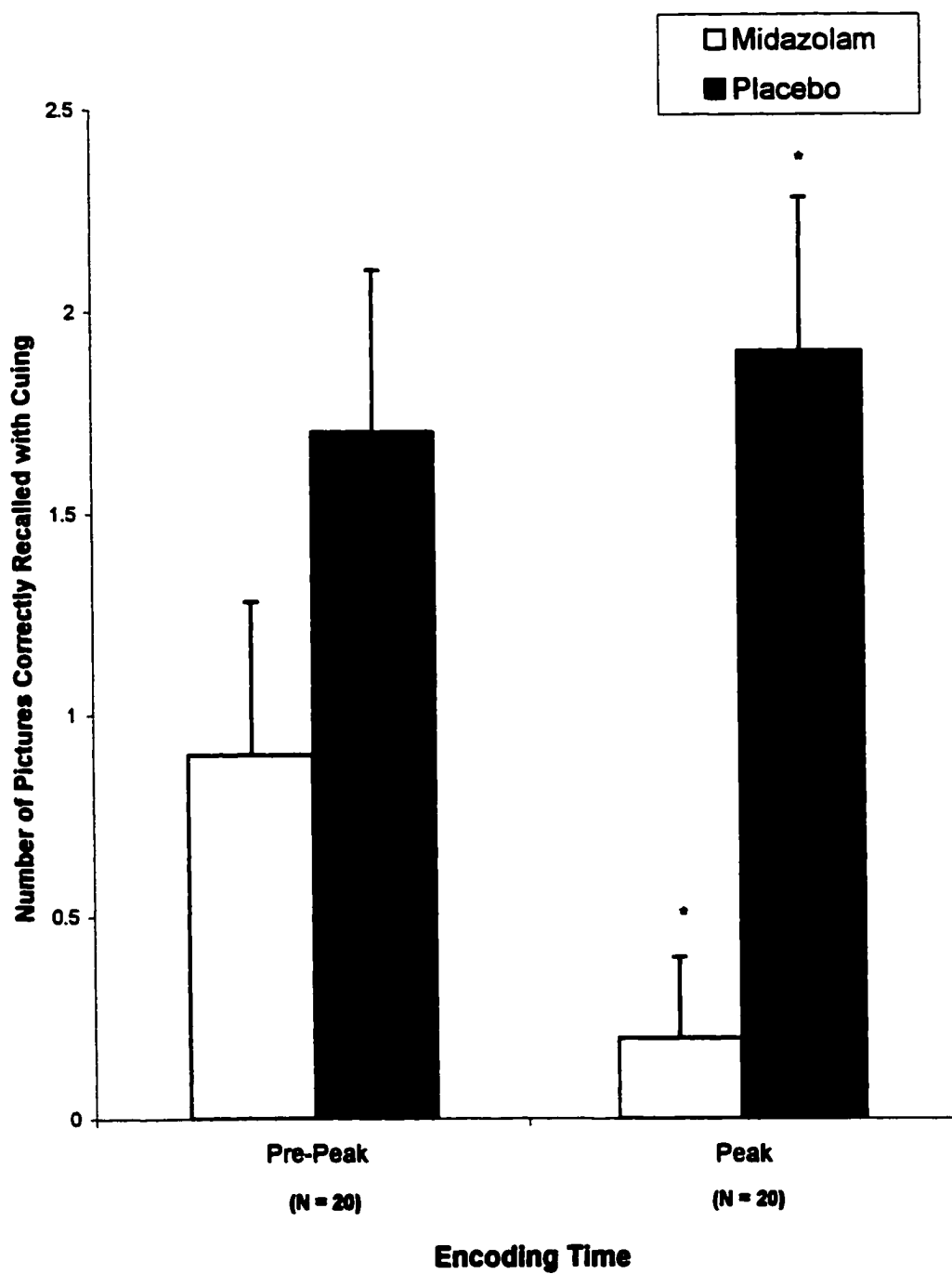


Figure 12: Cued Recall Performance: Mean number of pictures correctly recalled on the cued recall test as a function of Drug Group, at each Encoding Time (post-surgery period). Bars represent standard errors. Asterisk (*) indicates significant difference between Drug Groups.

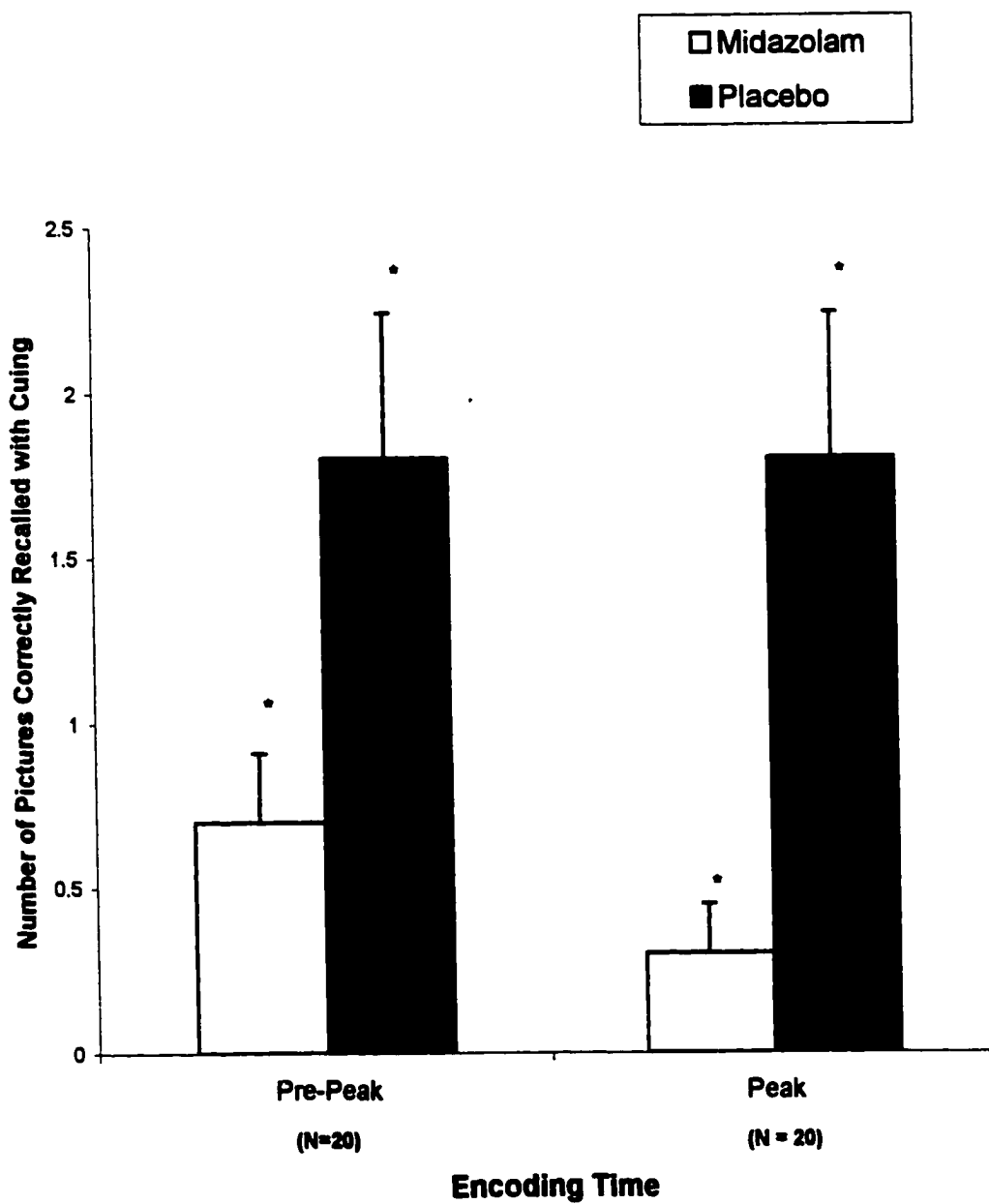


Table 10
Means (and SDs) for the Total Number of Pictures Generated on the Cued Recall Task as a Function of Drug Group and Encoding Time.

	Drug Group			
	Placebo		Midazolam	
Encoding Time (min. post-drug administration)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)
Words Generated (pre-surgery)	3.40 (2.01)	4.00 (2.31)	2.60 (2.32)	2.70 (2.06)
Words Generated (post-surgery)	3.90 (2.38)	4.00 ^a (2.31)	3.40 (2.63)	2.30 ^a (1.64)

Means with similar superscripts are marginally different from one another: ^ap = .056

Implicit Memory. The implicit memory test was scored as the number of primed pictures named as opposed to unprimed pictures. For the same reasons noted above for the explicit (cued recall) task, and because I had a priori time course predictions for priming performance, implicit memory scores were analyzed separately at each Encoding Time (Pre-Peak and Peak) and Testing Period (Pre- and Post-Surgery). These separate analyses each used a 2 x 2 (Drug Group x Priming Level) repeated-measures ANOVA. Means (and SDs) for the primed and unprimed tasks as a function of Drug Group at each Encoding Time and Testing Point, are displayed in Table 11. For pre-surgery implicit memory testing, there were no significant main effects of Drug Group at either the pre-peak or peak encoding times ($F(1, 18) = .09$; n.s.; $F(1, 18) = .13$; n.s., respectively). There was also no significant priming level main effect ($F(1, 18) = 3.10$, n.s.; $F(1, 18) = 0.53$, n.s., respectively) nor Priming Level x Drug Group interaction ($F(1, 18) = 0.19$, n.s.; $F(1, 18) = 0.00$, n.s., respectively). Likewise, at the post-surgery testing time, there were no significant main effects of Drug Group at either the pre-peak and peak encoding times ($F(1, 18) = .12$, n.s.; $F(1, 18) = 2.71$, n.s., respectively). There was also no Priming Level main effect for the 5 minute or 20 minute participants at the post-surgery testing time ($F(1, 18) = 1.80$, n.s.; $F(1, 18) = .89$, n.s., respectively). There were also no interactions at the post-surgery testing time for the 5 min or 20 min participants.

Further simple effects analyses indicated that the implicit task did not adequately assess priming. The placebo-treated participants did not show significant priming at either the pre-surgery ($F(1, 9) = 1.00$, n.s. [5 min]; $F(1, 9) = .26$, n.s. [20 min]), or post-surgery ($F(1, 9) = .31$, n.s. [5 min]; $F(1, 9) = 1.38$, n.s. [20 min]) testing times. This suggests that the task was not an adequate measure of implicit memory in the hospital

setting (see Table 11). When compared with the pilot participants, the placebo participants in the study showed similar performance in naming unprimed pictures (.75 – placebo-treated participants and .50 – pilot participants). However, the primed performance of the placebo treated participants was dampened relative to the pilot participants (.92 and 2.80, respectively). Overall, the performance of the placebo-treated hospital participants indicates that implicit memory task performance was not elevated above chance levels by prior experience.

Table 11

Implicit memory performance: Mean Number of Target Pictures Named on the Unprimed and Primed tasks, as a function of Drug Group at each Encoding Time and Testing Point.

	Drug Group			
	Placebo		Midazolam	
Encoding Time (min. post-drug administration)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)
Pre-Surgery Testing Point:				
Primed - Number of targets named	1.00 (.94)	.70 (.95)	1.0 (.94)	.60 (.52)
Unprimed - Number of targets named	.70 (1.06)	.90 (.87)	.50 (.53)	.80 (1.03)
Post-Surgery Testing Point:				
Primed - Number of targets named	.80 (.92)	1.20 (1.03)	1.10 (1.29)	.60 (.84)
Unprimed - Number of targets named	.60 (.70)	.80 (.79)	.50 (.71)	.50 (.71)

Observer-Rated Sedation. An initial examination of the observer-rated sedation scores indicated that at both testing times (pre- and post-drug), all participants were rated on the 5-point Likert scale as either a “3” (calm) or a “4” (drowsy). Therefore, the observer-rated sedation scores were analyzed as a categorical variable (rather than a continuous measure) using a four-group (midazolam pre-peak, midazolam peak, placebo pre-peak, placebo peak) Chi-Square analyses. Since there was no variation in scores at the pre-drug testing time (all 40 participants received scores of “3” [calm]), only data from the post-drug testing time was analyzed. At the post-drug testing time (immediately after memory task encoding), there was a significant difference between the 4 groups ($\chi^2(3) = 13.3, p < .005$) with 4 of the 40 participants rated as a “4” (drowsy) and the rest as “3” (calm). All the participants rated as drowsy were in the midazolam/20 minute group. A second, independent observer who was also blind to each child’s drug group membership provided ratings for a random 10 of the 40 participants (25% of the total sample). The inter-rater reliability coefficient could not be calculated at the pre-drug testing time due to the lack of variation in scores (all children were rated as calm by both observers). At the second testing time, the reliability coefficient was 1.00, indicating perfect agreement on this measure.

Objective sedation. The time taken for the child to complete the objective sedation task was analyzed with a 2x2x2 ANOVA (Drug Group x Encoding Time x Drug Phase [pre- vs. post- drug]). The ANOVA indicated a significant main effect of Drug Phase ($F(1, 36) = 10.86, p < .005$) and a significant effect of Drug Group ($F(1, 36) = 7.32, p < .01$). There was no significant main effect of Encoding Time ($F(1, 36) = .32, n.s.$) nor interactions involving the Encoding Time (pre-peak vs. peak) factor. There was a significant

interaction between Drug Group and Drug Phase ($F(1, 36) = 10.94, p < .005$). Simple effects tests indicated no significant effect of Drug Phase for the placebo subjects ($F(1, 18) = 0.00, n.s.$). For the midazolam-treated participants, there was a main effect of Drug Phase ($F(1, 18) = 11.14, p < .005$) with the participants taking much longer to complete the task at the post-drug testing time than the pre-drug testing time (see means and SDs in Table 12).

Table 12
Means (and SDs) on the Objective Sedation Task as a Function of Drug Group and Drug Phase.

Drug Phase	Drug Group	
	Placebo (n=20)	Midazolam (n=20)
Pre-Drug - Time (sec.) to complete MDT	55.55 (21.34)	57.05 ^a (21.86)
Post-Drug - Time (sec.) to complete MDT	55.40 (26.32)	131.70 ^a (106.18)

MDT, Motor Deletion Task (Corkum et al., 1995); Means with similar superscripts are significantly different from one another (^ap<0.005).

Attention Tasks. A series of 2x2x2 (Drug Group x Encoding Time x Drug Phase [pre- vs. post-drug]) ANOVAs were conducted on the time taken to complete the attention task, as well as the number of omission and commission errors on the task. The ANOVA on the time taken to complete the PDTP indicated a main effect of Drug Group ($F(1,36) = 6.45, p < .05$), and a main effect of Drug Phase ($F(1,36) = 10.31, p < .005$). The main effect of Encoding Time was not significant ($F(1,36) = 1.21, n.s.$) nor were any interactions involving Encoding Time. The ANOVA also indicated a significant interaction between Drug Group and Drug Phase ($F(1, 36) = 5.79, p < .05$). Simple effects analysis indicated that for the placebo participants there was no effect of Drug Phase ($F(1,19) = 2.28, n.s.$). However, for the midazolam participants there was a significant effect of Drug Phase with the participants taking longer to complete the task after receiving midazolam ($F(1, 19) = 8.50, p < .01$).

The ANOVA on the attentional omissions indicated a main effect of Drug Phase ($F(1,36) = 4.30, p < .05$). No other main effects were significant. In addition, there was a significant interaction between Encoding Time and Drug Phase ($F(1,36) = 4.72, p < .05$) and a marginal, three-way interaction between Drug Group, Encoding Time and Drug Phase ($F(1, 36) = 3.16, p = .084$). No other interactions were significant. Simple effects analysis indicated that neither of the placebo group (5 minute and 20 minute) showed an effect of Drug Phase ($F(1,9) = .08, n.s.$; $F(1,9) = 1.10, n.s.$, respectively). Likewise, the midazolam/5 minute group showed no significant difference in omission errors across Drug Phase ($F(1,9) = 1.00, n.s.$). However, the midazolam/20 minute group had a significant increase in omission errors at the Post-Drug Phase relative to the Pre-Drug Phase ($F(1,9) = 5.60, p < .05$).

The ANOVA on the commission errors indicated a main effect of Drug Group ($F(1,36) = 5.29, p < .05$) and a marginal effect of Encoding Time ($F(1,36) = 2.87, p < .10$). There was no main effect of Drug Phase and no interactions. Overall, the midazolam-treated participants had more commission errors than the placebo-treated participants, regardless of Drug Phase and Encoding Time. In addition, commission errors were most likely to occur for the participants in the 5-minute Encoding Time groups, regardless of Drug Group or Drug Phase. Although visual analysis of the data indicates that the midazolam participants in the 5-minute Encoding Time group demonstrated the most commission errors after drug administration, the crucial three-way interaction was not near significance ($F(1, 36) = .04, n.s.$). Moreover, the midazolam/5 minute group appears to have made more commission errors prior to drug administration as well, indicating that the four groups were not adequately balanced for commission errors at baseline. The means (and SDs) for the attentional measures are presented in Table 13, as a function of Drug Group and Encoding Time.

Table 13

Attentional Performance: a. Attention Speed, b. Attentional Omissions and c. Attentional Commissions, as a function of Drug Group at each Encoding Time.

	Drug Group			
	Placebo		Midazolam	
Encoding Time (min. post-drug administration)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)	Pre-Peak 5 (n = 10)	Peak 20 (n = 10)
a. Attention Speed				
- Time taken to complete PDTP				
Pre-Drug	45.40 (17.31)	44.10 (13.30)	43.80 (16.92)	50.60 (17.38)
Post-Drug	55.30 (18.49)	49.30 (20.50)	78.00 (49.53)	121.70 (102.29)
b. Attentional Omissions				
- Number of omissions on PDTP				
Pre-Drug	0.60 (1.58)	0.70 (1.57)	1.10 (1.52)	0.20 (0.63)
Post-Drug	0.90 (2.85)	1.40 (1.58)	0.70 (.95)	3.80 (4.73)
c. Attentional Commissions				
- Number of commission errors on PDTP				
Pre-Drug	0.50 (1.58)	0.10 (0.32)	1.40 (3.44)	0.00 (0.00)
Post-Drug	0.10 (.32)	0.30 (.67)	2.30 (3.86)	1.10 (1.97)

PDTP, Picture Deletion Task for Preschoolers (Corkum et al., 1995).

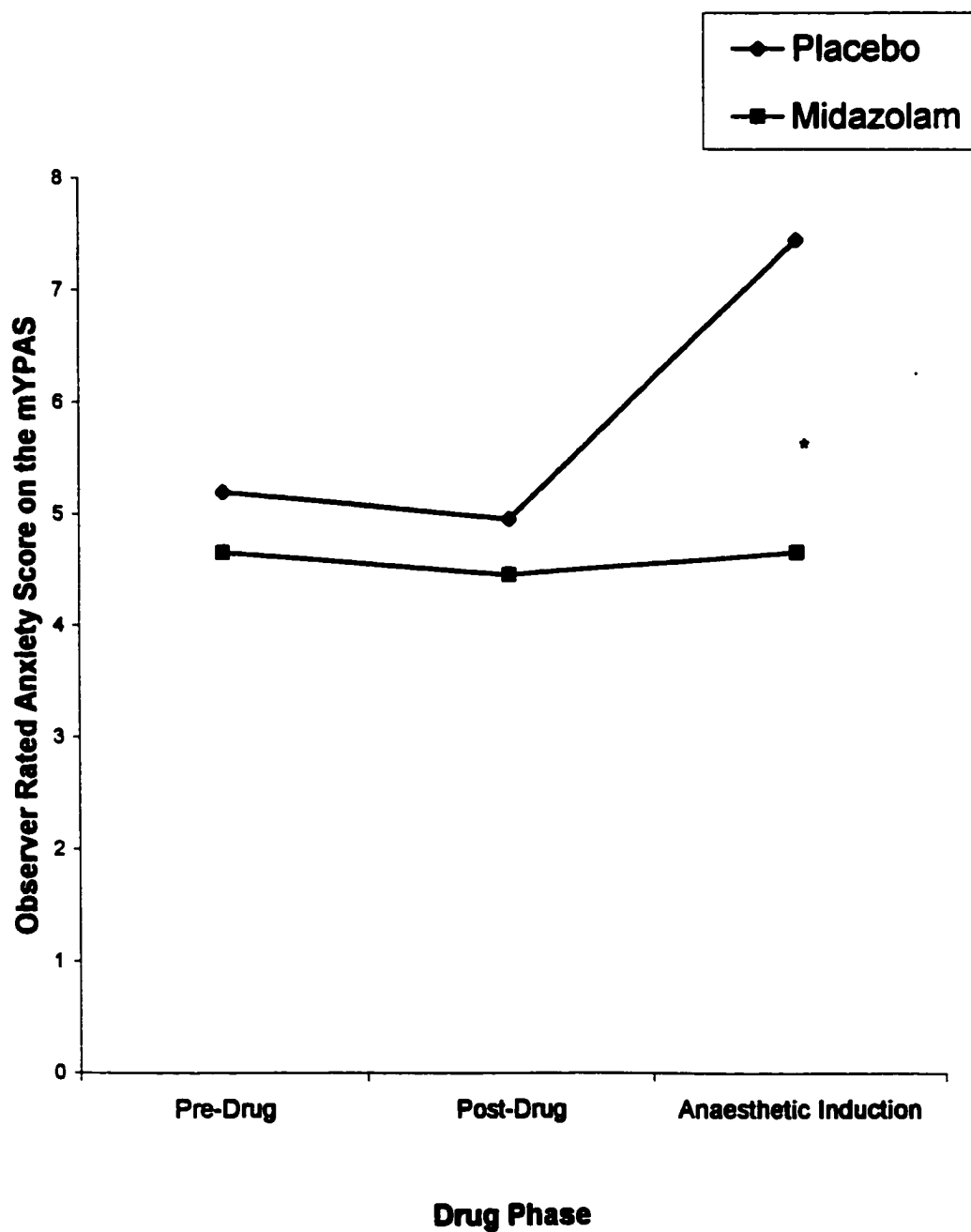
Observer Rated Anxiety. The approximate time between drug administration and entry into surgery was 50 minutes. It was possible that the two encoding time groups may have experienced differences in the amount of time elapsing between drug administration and surgery. For example, the 20-minute encoding time group may have been slightly delayed in entering surgery relative to the 5 minute post-drug encoding time group due to time taken to complete cognitive tests potentially delaying entry into surgery. One of the observer-rated anxiety measures was taken at the time of the anaesthesia induction in the surgery room. To ensure that this event occurred at a similar time post-drug for participants in all groups, the time that had elapsed between drug administration and the surgery was analyzed with a 2x2(Drug Group x Encoding Time) ANOVA. The ANOVA indicated no significant main effects of Drug Group ($F(1,39) = .01$, n.s.) or Encoding Time ($F(1, 39) = 1.7$, n.s.). In addition, there was no significant interaction between Drug Group and Encoding Time ($F(1, 39) = .37$, n.s.). This indicates that those in the 5 and 20 minute encoding groups entered surgery at similar time points following drug administration. Thus, the observer-rated anxiety data (mYPAS) were collapsed across levels of the Encoding Time factor. Then, mYPAS scores were submitted to a 2x3 (Drug Group [midazolam vs. placebo] x Drug Phase [pre-drug vs. post-drug vs. surgery]) ANOVA with repeated measures. This ANOVA indicated a main effect of Drug Phase ($F(1, 38) = 5.55$, $p < .01$) and a main effect of Drug Group ($F(1,38) = 5.96$, $p < .05$). In addition, there was a significant interaction between Drug Phase and Drug Group ($F(1,38) = 5.98$, $p < .05$). Simple effects analysis indicated that there was no Drug Group difference at the pre-drug phase ($F(1,38) = 1.48$, n.s.). Interestingly, there was also no Drug Group difference at the post-drug phase ($F(1,38) = .82$, n.s.). However, the

placebo-treated participants were significantly more anxious at anesthesia induction, as compared to the midazolam-treated group ($F(1,38) = 7.31, p < .05$). Further simple effects analysis indicated that there was no significant main effect of Drug Phase for the midazolam-treated participants ($F(1,19) = .00, n.s.$), suggesting that the anxiety levels of midazolam treated participants did not rise across the pre-drug, post-drug, and anesthesia induction portions of the study. However, there was a significant effect of Drug Phase for the placebo-treated participants ($F(1,19) = 6.83, p < .05$). Neuman-Keuls analysis revealed that the placebo-treated participants had higher levels of anxiety at the time of anaesthetic induction, as compared to their anxiety levels at both the pre-drug ($Q(3,19) = 9.80, p < .01$) and post-drug phase ($Q(2,19) = 10.92, p < .01$). There was no significant difference between anxiety at the pre-drug and post-drug phases ($Q(2,19) = 1.09, n.s.$) (see Figure 13). The second independent observer provided mYPAS anxiety ratings for a random 10 of the 40 participants (i.e., for 25% of the sample). The reliability coefficients ranged from 0.96 at both the pre-drug testing time and the time of anaesthetic induction, to 1.00 at the post-drug test phase, indicating excellent inter-observer reliability. Again, in the few cases of inter-rater discrepancy, I relied on my ratings in final scoring.

In addition to observer-rated anxiety, children's acceptance of the anaesthetic mask was rated as "calm", "frightened" or "hysterical" by the blind experimenter. Overall, the midazolam-treated participants were all rated as calm during anaesthetic induction. Three of the placebo-treated participants were rated as frightened and two were rated as hysterical. We used a one-tailed Chi Square test in evaluating significance of this effect given a priori predictions that midazolam would facilitate an easier anaesthetic induction. The Chi-square analysis indicated that the effect of Drug Group on

the rating received while the mask was placed on the child's face was significant ($\chi^2(2) = 2.5, p < .05$). A correlation between the child's observer-rated anxiety during anaesthetic induction and acceptance of the mask was highly significant ($r = .85, p < .0001$). This was expected because the child's behaviour at the time of mask placement was used in the determination of both the observer-rated anxiety scale and the rating of mask acceptance. A second observer provided ratings for mask acceptance for a random six of the 40 participants in the study (i.e., 15% of study participants). The inter-rater reliability coefficient for mask acceptance was 1.00, indicating perfect inter-rater agreement.

Figure 13: Observer-Rated Anxiety: Mean anxiety level as measured by the mYPAS as a function of Drug Group and Drug Phase. Bars represent standard errors. Asterisk (*) indicates significant difference between Drug Groups.



Covariation between cognitive impairments and performance on explicit memory tasks.

Free Recall. A series of analyses of covariance (ANCOVAs) were conducted which covaried out post-drug observer-rated sedation, objective sedation, and attention time, attention omissions and attention commissions, respectively from scores on the free recall for “under the influence of drug” surgery day events obtained on the day of surgery.

Although covariate-adjusted free recall memory means remained in the same direction as prior to covariance (i.e., midazolam < placebo), covarying out observer rated sedation appeared to reduce the Drug Group effects on free recall on the day of the surgery ($F(1, 37) = 3.71, p = .06$). Covarying objective sedation also appeared to reduce the Drug Group effect on the day of the surgery ($F(1,37) = 3.50, p=.07$). Covarying attentional time, omission errors and commission errors did not affect the pattern of the Drug Group effects or the significance level at the surgery-day testing time ($F(1,37) = 4.73, p<.05$; $F(1,37) = 4.43, p<.05$; $F(1,37) = 4.35, p<.05$, respectively).

Cued Recall (Explicit Memory). Similarly, ANCOVAs were conducted which covaried out post-drug observer-rated sedation, objective sedation, and attention time, attention omissions and attention commissions, respectively, from the scores on the explicit task (cued-recall) at the times that Drug Group effects were significant (20 minutes pre- and post-surgery and 5 minutes post-surgery). Covarying observer rated sedation scores did not affect the pattern of the post-surgery Drug Group differences or the significance levels of Drug Group effects on the post-surgery cued recall task for the 5 min participants ($F(1,17) = 5.01, p<.05$). For the participants tested at 20 minutes, the level of significance of the Drug Group effects for the post-surgery cued recall task appeared somewhat reduced, but remained statistically significant ($F(1, 17) = 8.75, p<.01$). At the

pre-surgery testing time, the level of significance was unchanged for the 20 min participants ($F(1,17) = 14.47, p < .001$). Covarying objective sedation (MDT scores) appeared to reduce the Drug Group effects on the post-surgery cued recall task for the 5 minute participants, but the effect remained marginally significant ($F(1,17) = 4.31, p = .05$). In addition, covarying objective sedation appeared to somewhat reduce the significance of the Drug Group effects on both the pre- and post-surgery testing times for the 20 minute participants. However, the Drug Group effects still remained statistically significant ($F(1,17) = 10.08, p < .01$; and $F(1,17) = 7.65, p < .05$ for pre- and post-surgery, respectively) and the pattern of the means was in the same direction. Covarying time taken on the PDTP for the 5 min participants appeared to reduce the significance level of the Drug Group effects on the post-surgery cued recall task, but the effect remained marginally significant ($F(1,17) = 3.39, p = .08$). Time taken on the PDTP also appeared to reduce the significance level of the Drug Group effects on the pre-and post surgery cued recall task for the 20 min participants. However, the Drug Group effects were still significant ($F(1,17) = 11.02, p < .005$; $F(1,17) = 6.55, p < .05$). Covarying omission errors for the 5 min participants did not affect the significance level or the pattern of Drug Group effects at the post-surgery testing time ($F(1,17) = 5.67, p < .05$). Covarying omission errors appeared to reduce the Drug Group effects on the pre- and post-surgery cued recall task for the 20 min participants. However, the Drug Group effects were still significant ($F(1,17) = 11.71, p < .005$; $F(1,17) = 10.71, p < .01$). Covarying commission errors appeared to reduce the significance level of the post-surgery Drug Group effects for the 5 min participants. However, the effect remained marginally significant ($F(1,17) = 4.03, p = .06$). Finally, covarying commission errors did not effect the significance

level or the pattern of the Drug Group effects for the 20 min participants at either the pre- or post-surgery testing times ($F(1,17) = 15.4, p < .001$; $F(1,17) = 11.99, p < .005$).

Recovery Measures

As there was no difference in the time between drug administration and surgery time for the pre-peak and peak participants (see observer-rated anxiety section above), the recovery data were collapsed across levels of the Encoding Time factor. A series of one-tailed (Drug Group) t -tests were used because directional effects had been predicted a priori. This set of analyses indicated a significant difference between the Drug Groups in the time between drug administration and time to wake in the recovery room ($t(38) = 2.02, p < .05$) with the midazolam-treated participants taking approximately 14 minutes longer, on average, to wake. An analysis of the time taken between drug administration and leaving the recovery room (meaning the child was sufficiently alert and responsive to return to the day surgery room) indicated a significant effect of Drug Group ($t(38) = 2.49, p < .05$). Overall, the midazolam-treated participants remained in the recovery room for approximately 22 minutes longer, on average, than the placebo-treated participants. Each child was rated by the recovery room nurses as having a “smooth”, “restless” or “stormy” awakening. None of the participants were rated as having a “stormy” awakening. Six of the placebo-treated and 2 of the midazolam-treated participants were rated as restless when waking up, whereas the remaining participants were rated as having a smooth awakening. This pattern suggests the possibility that midazolam-treated children may have smoother awakening post-surgery. We used a one-tailed Chi Square test in evaluating significance of this effect given a priori predictions that midazolam would facilitate a calmer awakening. The Chi-square analysis indicated

that the effect of Drug Group on the rating received while waking up was marginally significant ($\chi^2(2) = 2.5, p = .057$). Interestingly, the child's observer-rated anxiety score and mask acceptance score were not highly correlated with the child's behaviour upon waking ($r = .23, n.s., r = .33, p < .05$, respectively). Although the correlation between mask acceptance and awakening was significant, behaviour during mask placement would only predict 10% of the variance in the behaviour when waking. However, it should be acknowledged that there was not a lot of variability in these measures to begin with because both are categorical measures; this may have led to an underestimation of the true relationship between mask acceptance and quality of child's awakening post-surgery. For the other categorical measures (need for pain medication, and "other" problems (e.g., nausea, anxiety, crying), we again used one-tailed Chi Square analyses given the a priori directional predictions. There was no significant effect of Drug Group on the number of children requiring pain medication upon waking ($\chi^2(3) = .10, n.s.$) or the number of children experiencing "other" problems ($\chi^2(3) = .54, n.s.$).

Post-Hospital Behaviour. A series of one-way (Drug Group) ANOVAs indicated no significant effect of Drug Group on the total score on the PHBQ ($F(1, 38) = 0.15, n.s.$) or on any of its subscales. Scores on the PHBQ indicated that, on average, children in each drug group experienced no change in their behavior, according to parental retrospective reports, in the week following their surgery experience.

Discussion

Even though the groups were equivalent on all pre-drug cognitive measures, the present study lends support to previous findings that BZs impair explicit memory (e.g., Danion et al., 1990). In addition, the present study supports the idea that explicit memory

impairment occurs before peak blood concentrations of BZs have been reached, as was noted in Study 2. At the pre-peak Encoding Time, BZs impaired explicit memory performance on the cued recall task. However, this impairment appeared to be somewhat stronger in magnitude for the peak Encoding Time group, suggesting that the impairment level continued to increase as blood levels of the drug were approaching their peak concentrations at the time of memory encoding. Unfortunately, in the present study it was not possible to test participants at a post-peak testing time for several reasons. First, with midazolam, most children are so highly sedated by 30 minutes post-drug that they would be unable to participate in the cognitive testing (Smith et al., 1981). In addition, due to the busy nature of the day surgery room, it would not have been possible to test participants for longer periods of time, as their bed was needed for other children. Children were also being prepared for surgery by 40 minutes post-drug administration (a possible post-peak testing time). Although it would be possible to administer midazolam at an earlier time pre-surgery to allow more testing times between administration and surgery, this would lead to children entering surgery well after the peak blood concentration of midazolam had been reached. The present study, where midazolam was administered 50 minutes prior to surgery, was largely compatible with typical hospital procedure where midazolam is timed prior to surgery to allow children to experience the maximal effects of the drug close to time of surgery (i.e., oral midazolam is usually administered between 20 and 45 minutes pre-surgery).

It should also be noted that with the explicit (i.e., episodic) memory task used in the current study has some potential for contamination from semantic memory processes due to the reliance on categorization used in this task. However, semantic memory is not

believed to be impaired by BZs (Fluck et al., 1998) so this would not explain the differences between the BZ and placebo groups in the current study. In the future, however, it would be interesting to investigate children's errors on this task to determine if any differences between the two drug groups occurred. If the errors tend to be category-specific intrusions and this tendency is not impaired by BZs such as midazolam, this would provide further support that the midazolam-induced impairments on the Greenbaum and Graf (1989) "explicit" memory task are not secondary to semantic memory impairments. It should be noted that error rates were low on this task in the present study, and thus a larger sample size and/or a more taxing task (with greater error potential) would be required in future research to test this notion.

In the present study the cued recall task was completed at two testing periods using the same set of encoding stimuli. The first testing period occurred shortly after encoding as in Studies 1 and 2. At the second testing period (approximately 130 minutes after drug administration), participants were theoretically no longer under the direct influence of midazolam (or at least blood levels would have been substantially reduced by this time) as the half-life of midazolam is approximately 100 minutes (Smith et al., 1981). As in Studies 1 and 2 with oxazepam and/or lorazepam, at the first testing period, drug (midazolam) effects on explicit memory (cued recall) were observed. The fact that this drug-induced impairment remained on the cued recall task at the post-surgery testing period provides further evidence that BZ-induced memory impairments are not the result of a retrieval deficit, but rather are the result of impairments occurring at the encoding and/or storage phases of memory processing (Brown et al., 1982; Gorissen et al., 1998).

An advantage of our conducting two periods of testing with the same set of encoding stimuli was that we could examine the above issue of which phase of memory processing was being disrupted by midazolam. However, our two periods involved repeated presentations of the same memory tests, and as has been noted previously, there are many difficulties with repeated memory testing. Although different stimulus categories were used as retrieval cues at the two testing times, the potential for explicit contamination of the implicit task and for practice effects is still increased at the post-surgery testing time. In addition, because we opted to use only the picture sets previously developed and tested by Greenbaum and Graf (1989), our design was not completely balanced. That is, the implicit primed category at the first testing period served as the explicit, cued category at the second testing period. Therefore, whether or not a given word was generated at the first testing period could influence whether or not it was consciously retrieved in the second testing period. In other words, children had another “practice trial” with target words correctly generated during the first testing period. At least six word sets would have been needed for a completely balanced design in the present study, whereas we had only four at our disposal (cf. Greenbaum & Graf, 1989). Despite these limitations, midazolam-induced cued recall impairments similar to those that were apparent at the post-surgery testing time, were also noted at the pre-surgery testing time. Therefore, Drug Group effects were still apparent at the first testing period when there was little potential for contamination and for the other confounds noted above for the second period (post-surgery) of memory testing.

Researchers have noted that traditional lab-based tests of memory may lack “ecological validity”. In other words, lab memory tests may not be representative of real-

world memory requirements (Curran, 1986). In the present study, children were also administered a free recall task for their memory of personal events that had happened to them in the hospital context. Therefore, the children's memory for salient, personally relevant, real-world events was being measured. This is similar to the traditional studies of midazolam and memory in the pediatric surgery context that simply assessed children's memory for surgery events (Feld, 1990; O'Boyle, 1987). The free recall test was given at the end of the surgery day and at the child's six-week follow-up appointment. Therefore, the test assessed memory for surgery events after the effects of the drug had likely worn off. On the free recall task in the present study, midazolam-treated participants remembered fewer hospital events that likely happened while under the influence of BZ/placebo, whereas the two groups remembered an equivalent number of hospital events that likely happened when the participant was not under the influence of BZ/placebo. These results again indicate that BZs affect explicit memory for events that occur while under the influence of the drug. They also show that BZ explicit memory impairments occur even for events that are highly salient (e.g., having mask placed on face) as opposed to only memory for pictures of possibly less salient, neutral items (such as those used in the cued recall task).

Another advantage of the multiple testing times used in the cued recall and free recall task is that it is possible to examine the effect of midazolam on memory decay. Interestingly, for both the cued recall and free recall explicit memory tasks, participants did not show much deterioration or decay in their memory over time, regardless of their Drug Group status. For both tasks, it would be expected that children would remember fewer pictures at the second testing time as compared to the first testing time, due to the

time and events that elapsed between the two tasks. This should be particularly true for the free recall task where six weeks had elapsed between the two periods of memory testing (post-surgery vs. follow-up). However, the decay in free recall performance was only slight for the placebo-treated participants in the current study. For the cued recall task, the difference in time between the two periods of memory testing (pre- vs. post-surgery) was more in the order of 1.5 hours and decay was not apparent. In an interesting study of children's memory for medical emergencies (Peterson, 1999) children were asked for their free recall of medical emergencies (e.g., broken bones, stitches) at several times in the two years after medical treatment. Overall, the children's memory of the accident and the hospital experience was stable over a 2-year follow-up. However, when broken down into memory for the injury itself and memory for hospital events, only the memory for the injury details remained stable. Perhaps, the entire surgery situation is also very salient for children and they are less likely to forget information encoded in the surgery context over time. The task used in the present study does not allow for a detailed examination of this idea as it was free recall (coded as yes/no for given category) rather than the more detailed cued recall used by Peterson (1999).

The virtual absence of decay of memories observed in the present study is consistent with what is known about trauma and memory. For example, among individuals with Post-Traumatic Stress Disorder, a key criterion of the disorder is difficulty forgetting an experience that is perceived to be traumatic (DSM-IV, 1994). The potentially "traumatic" nature of the events occurring in the context of surgery might explain the virtual absence of decay of memories in the free recall task. However, the cued recall task used in the present study (i.e., pictures of affectively neutral objects)

should not have been traumatic or aversive. It is possible that even neutral objects/events that occur when a child is in a frightening, unique or salient situation also tend to be better remembered. However, the results of the Peterson (1999) study of children's memory for hospital experiences does not support this hypothesis, since only injury information but not general hospital events were well remembered by her child participants over time. Further study is clearly needed in this area.

It should also be noted that memory on both the cued and free recall tasks in the present study actually tended to be relatively "poor" (between 10% and 30% correct recall) at the first of the two testing periods (see Table 9 and Figures 11 and 12), perhaps leading to a "floor effect" for memory decay. In other words, there was not much information to begin with that could decay over time. A possible explanation for the generally low levels of recall in the present study pertains to the fact that the memory tasks used were relatively taxing. On a free recall task it is unlikely that participants will generate all of the possible "targets". Also, the cues used in the "cued recall" task in Study 3 were category names as opposed to specific cues for each target word (like the word-stems used in Study 1 and 2). Researchers who wish to further examine memory decay in a paediatric surgery setting might want to use less taxing tasks to eliminate the above floor effects interpretation.

Unfortunately, it was not possible to examine the time-dependent effects of BZs on implicit memory in the present study. Although the pilot test participants did show significant priming in a similar fashion to the children studied in the original Greenbaum and Graf (1989) study, priming effects were not observed in the children in the hospital situation in the present study. In fact, priming among our hospital study participants was

absent even among placebo control participants whom we had expected would perform similarly to our pilots. Obviously, the most salient difference between the pilot study and the study proper is that the latter took place in a hospital context, whereas pilot testing occurred in participants' homes or in a university-based laboratory. Certainly, the hospital situation provided more distractions for participants (e.g., hearing other children cry). However, research suggests that divided attention should impair explicit memory, while having little effect on implicit memory (Rabinowitz et al., 1982).

Another possible explanation for the discrepancy is that the study participants may have been more anxious than the pilot-tested participants. Unfortunately, observer-rated anxiety scores were not conducted with the pilot participants, so it is not possible to determine if the pilots were less anxious than children in the hospital situation during cognitive testing. Although the study participants' anxiety levels had not increased significantly between the pre-drug and post-drug test phase (when the memory encoding took place), it is possible that they had arrived at the hospital in a more anxious state than was experienced by our pilot participants at the time of cognitive testing. In studies of memory for neutral vs. anxiety relevant stimuli in clinically anxious participants, results indicate that implicit memory for anxiety relevant stimuli is increased among anxious subjects relative to controls, while there is no such "negative bias" in anxious participants' explicit memory performance (e.g., Mathews, Mogg, May & Eysenck, 1990). However, implicit memory for neutral stimuli, such as the Greebaum and Graf (1989) pictures used in the present study, does not appear to be impaired in clinically anxious participants relative to controls. To my knowledge, no study has been conducted in which non-clinical participants were tested on implicit and explicit memory tasks using

neutral encoding stimuli following state anxiety induction. In the present study, correlations between observer-rated anxiety at the time of encoding and primed implicit memory performance (for placebo treated participants) at both the pre- and post- surgery testing times were not significant ($r = -.05$, n.s.; $r = -.28$, n.s.). Likewise, correlations between observer-rated anxiety at the time of encoding and a difference score created by subtracting unprimed from primed performance (for placebo treated participants) at both the pre- and post- surgery testing times were not significant ($r = -.06$, n.s.; $r = -.22$, n.s.) This finding suggests that anxiety, at least as rated by observers, did not appear to be significantly contributing to performance on the implicit memory task.

Another possible reason for the difference between the pilot participants and the study participants was that only the children in the study proper were dealing with chronic middle ear infections (Otitis Media). As I was aware that some of the participants in the study might have mild hearing loss, the study stimuli were primarily encoded visually. Also, if the child could not correctly name the picture, they were told the correct name and asked to repeat it to ensure the word had been heard. Although it was possible that the study participants were unable to hear the memory test instructions, it does not seem likely. First, if hearing loss was the reason for the pilot-study discrepancy, one would assume impairment across the board for both explicit and implicit memory performance. It is possible that the study participants had more difficulty understanding the longer instructions for the implicit memory task. However, this does not seem likely as study participants named items from the correct category (e.g, zoo animals when told the zoo story), but simply failed to name items that they had seen during encoding at greater-than-chance levels.

Research has been conducted to determine if otitis media leads to any specific cognitive impairment that might explain the pilot-study discrepancy. Most studies indicate that there are no long-term effects of otitis media on cognitive task performance (Roberts, Burchinal, & Clarke-Klein, 1995). However, one study indicated that children with a history of otitis media had difficulty listening to verbal material in the presence of background noise (Gravel & Wallace, 1992). Certainly, this might explain the difficulty that the study participants had with the longer, implicit memory stories that were presented in a situation with background noise. However, the Gravel and Wallace (1992) study examined children who all had recurrent ear infections before the age of one. Another study of children with a history of otitis media indicated that only children who are chronically affected in the first year of age have difficulties on cognitive tasks in the future (Teele et al., 1984). Unfortunately, we did not obtain information about the time of the child's first ear infections in the present study.

A final difference between the study participants and the placebo-treated group is that the study participants all received Tylenol™ before the memory testing. Although a review of the literature indicates that no studies of the cognitive effects of Acetaminophen have been conducted, the side-effect profile for Acetaminophen is believed to be virtually nonexistent (Canadian Pharmaceutical Association, 1999). Therefore, the possibility that Acetaminophen was responsible for the lack of priming shown in the study participants is highly unlikely. In the future, pilot testing should be conducted in the situation that the study will occur, to ensure that the tasks used will be effective measures of implicit and explicit memory in the particular context in which they are to be employed.

Analysis of the observer-rated sedation scores indicated a time-dependent increase in sedation. None of the participants were rated as sedated prior to drug administration, whereas more of the midazolam participants in the peak blood concentration condition were observer-rated as sedated following drug administration. However, even for the 20 min group, the majority of participants did not appear sedated to the observers. In contrast, the objective sedation measure indicated that the midazolam-treated participants were significantly sedated at both Encoding Times. This indicates a dissociation between observer-rated and objective sedation, in that most midazolam-treated children did not appear to be sedated at pre-peak testing, while their performance was quite impaired on an objective, psychomotor speed task. Thus, the chosen objective sedation measure appears more sensitive to midazolam impairments than the observer rating used in the present study. The results also suggest that participants appear outwardly sedated at a later time than one can observe impairments on a psychomotor task. It would be interesting to attempt to replicate this finding with adults, using an observer-rated sedation measure. If the finding was replicated with adults, it would have implications for driving in that midazolam-treated individuals might be deemed fit to drive based on behavioral observation, when they would actually have impaired reaction time.

One problem with the observer-rated sedation scale used in the current study is that only two of the five anchors were ever used in the study (calm and drowsy). This suggests the need for a more fine-grained measure within those two points to increase sensitivity to subtle differences in sedation in this kind of research. A second problem with the sedation scale used in the current study (and those used in anaesthesia research

in general) is that it is likely to be confounded by anxiety, in that “agitated” and “alert” are rated when a child is crying or clinging to his/her parent. In the future, a new sedation measure should be created which adds more fine-grained points and which makes a better conceptual distinction between sedative and anxiolytic drug effects. In other words, to ensure that only sedation is being rated, a child who is calm should be rated as “non-drowsy”, as should a child who is crying but does not appear sleepy. It would also be helpful to develop a child-rated sedation scale, to maintain consistency with adult studies on the subjective sedative effects of BZ administration.

An analysis of the effects of midazolam on attention led to some very interesting results. Overall, on time taken to complete the PDTP, midazolam participants were impaired relative to placebo at both encoding times. This result parallels the findings with the MDT (objective sedation) where midazolam participants were impaired relative to placebo at both pre-peak and peak encoding times. This parallel is not surprising given that BZ-induced “attentional” impairments on deletion tasks are likely to be confounded with psychomotor speed impairments (Curran et al., 1993b). However, time course effects were noted for the other attentional measures. Only the midazolam participants tested around the time of peak blood concentration of midazolam had significantly more omission errors, indicating a time-dependent impairment in focussed attention. Interestingly, all midazolam participants had increased numbers of commission errors, but the pre-peak participants appeared to have the most. It is possible that midazolam may lead to an early “disinhibiting” effect as blood levels of midazolam are first beginning to rise. However, this interpretation requires further investigation as the pre-

peak midazolam group also had a higher baseline rate of commission errors in the present study, despite random assignment of participants to study groups.

In an attempt to rule out the possibility that the midazolam-induced impairments in sedation and/or attention were primarily responsible for the memory impairments in the current study, a series of ANCOVAs were performed. Although it appeared that sedation and attention did have some contribution to BZ-induced performance impairments on the explicit cued recall and the free recall memory tasks (cf. Bishop & Curran, 1995), all Drug Group differences remained significant or marginally significant, indicating that the memory effects were not simply the result of other cognitive impairments. These findings are consistent with the findings of previous basic cognitive psychology literature in indicating that attention and arousal contribute to explicit memory performance, but do not fully account for explicit memory effects (e.g., Rabinowitz et al., 1982; see also review by Roediger & McDermott, 1993).

Overall, the placebo-treated participants became more anxious at the time of surgery than the midazolam-treated participants. This finding is consistent with previous studies of oral midazolam in a surgery context (Cray et al., 1996; Feld et al., 1990; Kain et al., 1999). Midazolam appeared to prevent the elevation in anxiety observed in non-drugged controls during anesthetic induction. Interestingly, the anxiolytic effect of midazolam was not observed at the post-drug testing time (5 or 20 min. post-drug). This lends support to the idea that anxiolytic effects of BZs are only observable at times of heightened anxiety (i.e., anxiety is not reduced by BZs in individuals who are already calm or only mildly anxious) (cf., Golombok et al., 1991). In addition, only placebo-treated but not midazolam-treated participants were rated as “frightened” or “hysterical”

when the mask was placed on their face. These children often struggled or attempted to pull the mask off their face, indicating that midazolam makes the induction process easier for both the child and the anaesthesiologist. However, it should be noted that even the majority of placebo-treated participants (i.e., 80%) had a calm induction of anaesthetic on the 3-point observer-rated scale, indicating that only a small number of children may actually benefit in this manner from midazolam pre-treatment.

In addition, more placebo-treated than midazolam-treated participants were upset upon waking. As mentioned previously, participants' behaviour when waking was not strongly related to their behaviour and anxiety level during mask induction. Therefore the greater upset upon waking in the placebos was most likely because they woke earlier than the midazolam-treated children. Thus, the placebo children were more likely to have been upset by the dizzy feelings still being caused by the anaesthetic. Anaesthetic effects most likely had worn off further when the average midazolam-treated child woke, given the significantly later awakening among midazolam treated participants relative to placebo controls. However, as with the child's acceptance of the mask, the majority of the placebo-treated participants (i.e., 70%) had a "smooth" awakening, indicating that not all children would benefit from this aspect of midazolam pre-treatment.

Although midazolam eases induction and waking in the recovery room, it is likely that the administration of midazolam to all children as a preoperative medicant would lead to a bottle-neck in the recovery room, as the midazolam-treated participants remained in the recovery room for 22 minutes longer than the placebo-treated participants. In a busy recovery room, other children would be returning from surgery and needing the beds taken up by the sleeping children. The 22 minute increased stay in

the recovery room is much longer than the difference reported in some previous studies (e.g. Weldon et al., 1992 – no difference) and similar to other studies (Cray et al., 1996 – 11 minutes to eye opening and 30 minutes increased stay in recovery room). The discrepancies in the literature are most likely a result of midazolam being administered at variable times pre-surgery in each study and the fact that previous studies used surgeries of variable lengths. Myringotomy surgery is a very quick procedure. This would result in a prolonging of the effect of midazolam on recovery, as the sedative effects of the drug would not have completely dissipated by the time the child had left surgery.

In the future, research should be conducted to determine what variables might be predictive of a difficult anaesthesia induction or recovery, thus indicating the need for pre-operative midazolam treatment. Such variables might involve aspects of a child's temperament (e.g., emotionality; Buss & Plomin, 1984), initial anxiety levels at hospital admission (Badner et al., 1990), or even parental anxiety levels (Bevan et al., 1990).

Although the placebo-treated participants were more anxious at the time of anaesthetic induction and displayed a more difficult acceptance of the mask and a more stormy recovery upon awakening from surgery, parental reports did not indicate any difference between the groups upon return home after surgery. This is in contrast to previous studies that found increased behavioural problems in placebo-treated participants relative to midazolam-treated participants (Kain et al., 1999; McCluskey & Meakin, 1994). Unfortunately, the PBHQ was completed by parents at the child's six-week follow-up appointment with their surgeon. It is quite possible that parents may have forgotten or minimized by then any small changes in their child's behaviour that occurred in the week following the surgery. In the future, the PBHQ should be

completed at the end of the first post-surgery week, or even better, prospective measures should be used following the child's discharge from hospital to avoid problems associated with retrospective recall (Sobell & Sobell, 1990). Of course, the advantages of this prospective methodology might be offset by poor parental compliance with the requirements of daily child behavior monitoring.

Overall, it appears that midazolam leads to impairments in explicit memory, as well as inattention and increased sedation, with some of these cognitive effects increasing in magnitude with increasing blood levels of drug. In addition, midazolam decreased children's anxiety during anaesthesia induction and lead to an easier induction. Thus far, in the anaesthesia literature, amnesia and decreased anxiety on the day of surgery has always been described in positive terms. However, animal studies with BZs have indicated that BZs may actually hinder the effects of exposure, in that extinction of anxiety does not occur (Boix, Fernandez Teruel, & Tobena, 1988). In other words, since the midazolam-treated participants in the present study have a poor memory for the events leading up to surgery, their poorer memory may interfere with habituation of anxiety (as a midazolam-treated child may not remember that his/her worst fears were not realized). Thus, it is possible that children who received midazolam as a pre-operative medicant in the surgery context, would actually be more fearful during a second (repeat) surgery than the children who received placebo. Although the placebo-treated children were more fearful than midazolam-treated children during the present study, placebo-treated children demonstrated greater memory for events occurring close to the time of the surgery. The placebo-treated participants' greater memory for their exposure to "fearful" stimuli without negative consequences (e.g., exposed to surgery without

significant pain), would likely lead to greater habituation in the placebo vs. midazolam group over time. This drug group difference in habituation might be observed if anxiety observations were made on these same children in the surgery context again in the future.

A study of flight phobics supports this hypothesis of differential drug group effects on the longer-term efficacy of exposure (Wilhelm & Roth, 1997). In this study, flight phobics were administered alprazolam or placebo before flying. Drug administration was timed so that the BZ would be at peak blood levels at the time of flight take-off. The results indicated that the participants who received alprazolam were less anxious than placebo-treated participants during the first flight, similar to the present findings of decreased anxiety during a stressful event (anaesthetic induction prior to surgery) among children receiving midazolam vs. placebo. However, on a second flight, when all participants received placebo, the individuals who previously received alprazolam were more anxious and were more likely to experience a panic attack than those who had previously received placebo. In the present study, it is possible that the children who received midazolam might be more likely to be anxious during future anaesthesia induction.

Certainly, it would be easy enough to continue giving children midazolam at future surgeries. However, it is possible that BZs would diminish the development of self-efficacy in that children who felt that they needed “medicine” to deal with the surgery process might begin to view other anxious situations as beyond their personal control (Westra & Stewart, 1998). These children might become more anxious in other similar situations such as doctor’s and dentist’s visits (i.e., generalization). In addition, if future research does show placebo-treated participants to be less likely than midazolam-

treated participants to be anxious during a subsequent surgical procedure (as a result of habituation in the placebo group) it would not seem appropriate to routinely administer BZs as preoperative medicants. This is particularly true considering the problems with the potential “bottle-neck” in the recovery room observed in this and other studies (e.g., Cray et al., 1996).

Future studies should examine the interaction of BZ time-course with surgery exposure. For example, using a design similar to that of Wilhelm and Roth (1997), surgery-naïve and BZ-naïve children could first be given a 0.50 mg/kg dose of midazolam or placebo at three different time points, so that anaesthetic induction occurs at pre-peak, peak or post-peak levels of the drug. Next, all children should be given placebo at the time of a second surgery to examine the drug group differences in anxiety levels at the time of anaesthetic induction, and whether time-course interacts with hypothesized drug effects. Based on the time course results of this thesis and the results of Wilhelm and Roth (1997), it could be hypothesized that at the second surgery, participants previously pre-medicated with midazolam would show greater anxiety than those previously pre-medicated with placebo, particularly those in the “peak” group (where midazolam’s memory dampening effects should be maximal). Obviously, this study would require participants who are likely to have repeat surgeries. Repeat surgeries are common in children receiving ear tubes, as ear tubes tend to fall out after a few years (Iwaki et al., 1998; Schilder et al., 1997).

In future studies, it is important that the time-dependent effects of midazolam on implicit memory in children are also studied. Certainly, it is apparent that the Greenbaum and Graf (1989) implicit memory task did not lead to priming for several possible reasons

(although the exact reason has not yet been determined). It would be interesting to pilot test another implicit memory task with children who are receiving ear tubes. Another implicit memory test that appears well-designed is the Bullock-Drumme and Newcombe (1995) task in which children read a picture book with the examiner, and are later shown the same pictures in progressively less blurry forms and asked to identify them (similar to the degraded pictures priming measure used in the adult literature; see review by Roediger & McDermott, 1993). This task was not chosen in the current study for practical and methodological reasons. First, it would not be easy to use an overhead projector in a busy day surgery ward. However, to overcome this limitation in future, the blurry pictures could be printed out on paper and shown to children in this form, or a small laptop computer could be used to project the blurry images. A second problem with the study is that a popular children's book was used to obtain the encoding stimuli. Obviously, if a child had previously encoded the stimuli, midazolam would not be expected to impair their memory of the pictures, as BZs do not cause retrograde amnesia. A positive aspect of the book is that the author of this book has written three books containing a total of 30 pictures of animals. This increased number of stimuli would make it possible to conduct repeated testing without having to reuse stimuli. However, only "naïve" children who had never been in contact with the books could be used in such a study.

Overall, more research is needed in the area of BZs in conjunction with paediatric surgery. It will be important for the relative time course of midazolam's effects on implicit and explicit memory to be determined to aid anaesthesiologists in determining the most effective time to administer the drug before the surgery begins. In addition,

research is needed to determine which children would actually benefit from midazolam pre-medication, or whether alternatively midazolam-induced memory impairments might be counter-productive in the longer term (cf. Wilhelm & Roth, 1997). Finally, as discussed above, research is needed to determine how midazolam pre-medication affects anxiety about future surgery or other medical procedures, and how precisely anxiety and memory may be inter-related.

CHAPTER SEVEN: General Discussion

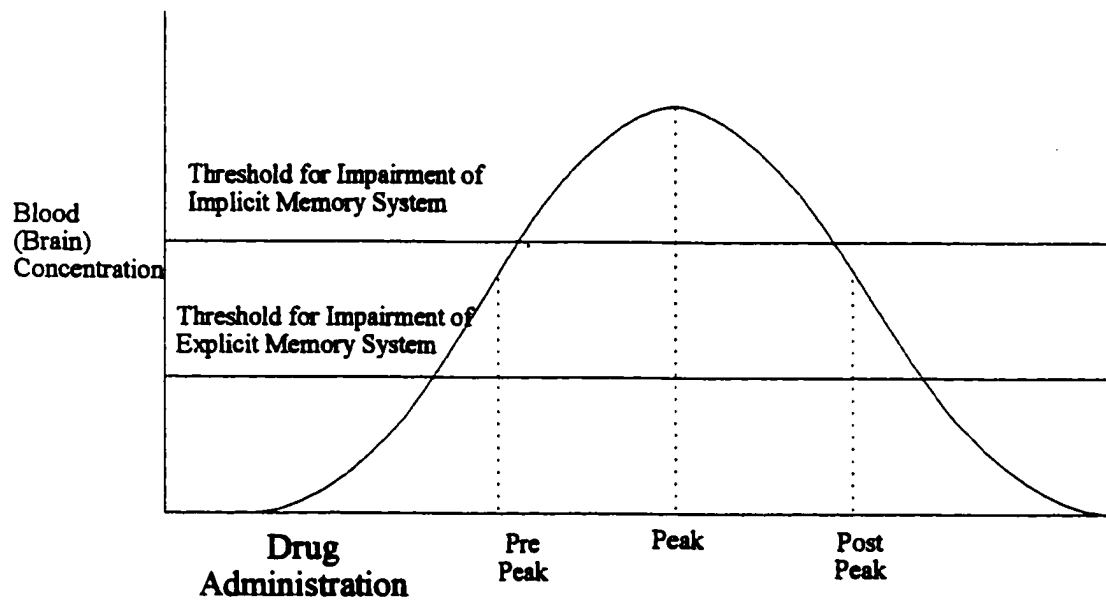
The Objective of This Line of Research

The primary objective of this line of research was to advance knowledge of the time-dependent effects of BZs on implicit and explicit memory. In 1996, Stewart and associates provided preliminary data which indicated that both oxazepam and lorazepam may impair implicit memory, but in a time-dependent fashion. Study 1 was designed to replicate these findings after overcoming several limitations of the original study. To determine if BZs impair both implicit and explicit memory if tested at the time of peak blood concentration of the drug, participants were administered lorazepam, oxazepam or a placebo and memory encoding took place at a time point which was close to the theoretical peak blood concentration of oxazepam (30 mg). Study 2 was designed to more fully examine the time-course of the effects of a single BZ (oxazepam, 30 mg) on implicit and explicit memory. Participants were administered oxazepam or a placebo and memory encoding took place at one of three time points post-drug administration: before the peak blood concentration of the drug (“pre-peak”), close to the peak blood concentration of the drug (“peak”), or after the peak blood concentration of the drug (“post-peak”). Finally, Study 3 was designed to examine the time-dependent effects of BZs on implicit and explicit memory in a clinically relevant setting. Children who were undergoing myringotomy surgery were administered midazolam or placebo and encoded stimuli for use in implicit and explicit memory tasks at either a pre-peak or peak testing time.

Implicit Memory

Overall, Studies 1 and 2, using two BZs (oxazepam and lorazepam) at a variety of time-points, lend support to the idea of time-dependent effects of BZs on implicit memory. That is, BZs appear to impair implicit memory when plasma levels reach a specific threshold concentration. At least for the particular BZs and doses tested in this thesis, this threshold concentration appears to occur at a time when a given BZ is reaching its peak blood concentration (see Figure 14). The results of Study 2, using oxazepam (30 mg), indicate that implicit memory is not impaired if memory is tested before the peak blood concentration of a BZ has been reached (see Figure 14). However, if memory encoding occurs around the time of peak blood concentration of the drug, implicit memory is impaired by BZs, as the threshold concentration of oxazepam needed to impair implicit memory has been crossed (see Figure 14). At the post-peak testing time in Study 2, implicit memory impairments were marginal suggesting that they may have begun to wane (see Figure 14). However, this latter finding needs to be replicated, as the placebo-treated participants in Study 2 had decreased performance at the post-peak testing time, likely contributing to the diminished drug group difference. Unfortunately in Study 3, the implicit task utilized (i.e., Greenbaum & Graf, 1989) did not adequately measure priming in a hospital setting. Even participants who received a placebo did not show priming on the implicit memory task. Future studies should examine different paediatric implicit memory tasks after pilot testing them in the situation that the study will be conducted, prior to evaluating time-dependent drug effects on performance on such tasks.

Figure 14: A Visual Depiction of the Theoretical Relationship Between Plasma Levels of the Drug and Explicit and Implicit Memory Impairment Thresholds.



Recently, researchers have begun to distinguish between two types of priming in implicit memory paradigms (Tulving & Schacter, 1990): perceptual and conceptual priming. Perceptual priming is the most commonly studied type of priming. It is said to occur when prior exposure to a stimulus facilitates the participant's ability to later identify the same stimulus perceptually when relevant cues are presented (Bishop & Curran, 1998; Tulving & Schacter, 1990). Examples of tasks tapping perceptual priming include word stem completion (e.g., Studies 1 and 2) and degraded pictures. In contrast, conceptual priming occurs when a participant is presented with a cue that is conceptually related to a previously encoded stimulus (Roediger & McDermott, 1993). For example, a participant might encode a word list that includes the word "elephant". Later, when asked to name an animal, he/she might be more likely to say "elephant" than to name an animal to which he/she had not been previously exposed. Therefore, semantic processing must be involved in priming in this case, as there is no perceptual similarity between the original stimulus ("elephant") and the cue presented ("animal") (Bishop & Curran, 1998). The Greenbaum and Graf (1989) methodology used in Study 3 is a conceptual priming task, as opposed to the perceptual priming tasks used in Studies 1 and 2. Researchers suggest that conceptual priming is based on the semantic memory system, which assesses knowledge, whereas perceptual priming is based on the perceptual representation system (PRS), which assesses the structure and form of stimuli (e.g., Tulving & Schacter, 1990). Studies indicate that conceptual and perceptual priming can be dissociated by factors such as age (Jelicic, Craik, & Moscovitch, 1996), supporting the hypothesis that they are distinct memory processes subserved by dissociable memory systems.

Very few studies have examined the effects of BZs on conceptual priming. However, one recent study of conceptual priming (category generation task) indicated that it was not impaired by administration of a clinical dose of lorazepam (examined at two hours post-drug) (Bishop & Curran, 1998). This is in contrast to other studies that have found impairments in perceptual priming assessed at the same encoding time with the same BZ (Bishop et al., 1996). Another recent study compared the effects of a clinical dose of lorazepam on a conceptual (word association) and a perceptual (word identification) task. Results indicated that perceptual priming was impaired by lorazepam, relative to placebo-treated participants. However, the lorazepam-treated participants did not show impaired performance, relative to the placebo group, on the conceptual priming task (Thompson, Stewart, & MacPherson, 1999). In addition, other studies have found that divided attention may impair conceptual priming, but does not affect perceptual implicit memory (Schmitter-Edgecombe, 1999). These findings of differential impairment of conceptual and perceptual priming lend further support to the view that perceptual and conceptual priming processes are subserved by two different memory systems (Tulving & Schacter, 1990).

Based on the results of these recent studies, it is possible that even if the Greenbaum and Graf (1989) implicit task was an adequate measure of priming in a surgery environment, midazolam may not have impaired implicit memory on this conceptual priming task as we had originally hypothesized. Certainly, the fact that BZs may not impair conceptual implicit memory does not explain the findings in Study 3, as both midazolam and placebo-treated participants failed to show priming, whereas non-medicated participants in the Greenbaum and Graf (1989) study and non-medicated pilot

participants in Study 3 did evidence priming. However, Schmitter-Edgecombe's (1999) findings that conceptual priming is impaired by divided attention manipulations may play a role in explaining our failure to observe priming in the hospital/surgery setting. It is possible that the distractions evident in the hospital environment may have interfered with participants' conceptual priming performance. In light of the recent findings regarding the effects of BZs on perceptual vs. conceptual priming (Bishop & Curran, 1998; Bishop et al., 1996; Thompson et al., 1999) future studies of midazolam in paediatric surgery settings should use a developmentally-appropriate perceptual priming task (e.g., the blurry pictures task; Bullock-Drummey and Newcombe, 1995) to maintain consistency with the word-stem completion perceptual priming task most commonly used in adult studies (cf., Studies 1 and 2). However, it would also be very interesting to use both a conceptual and a perceptual priming task in the same study, in an attempt to replicate and extend to children Thompson and associates' (1999) findings of a BZ-induced dissociation between perceptual and conceptual priming among adults.

Explicit Memory

Overall, the results of Studies 1, 2, and 3 support the abundance of research that suggests that BZs impair explicit memory (Allen et al., 1991; Bishop & Curran, 1995). It also appears that explicit memory impairments begin earlier than implicit memory impairments following an acute dose of BZ (see Figure 14). It appears that a lower concentration of BZ is required to obtain explicit memory impairments relative to implicit memory impairments (see Figure 14). Therefore, BZ-induced explicit memory impairments are observed over a longer time span relative to implicit memory impairments (see Figure 14). In both Studies 2 and 3, explicit memory impairments were

apparent at the pre-peak testing time, while implicit memory impairments did not appear until the peak testing time (Study 2). The results of Study 3 indicate that explicit memory impairments continue to increase as the blood concentration of midazolam rises.

However, in Study 2, explicit memory impairments with oxazepam were relatively stable across encoding times. It is possible that the pre-peak testing time used in Study 3 with midazolam is relatively earlier (i.e., corresponds to a relatively lower concentration of BZ) than the pre-peak time used in Study 2 with oxazepam. Although midazolam is more fast-acting than oxazepam, the five minute testing time for midazolam might not be equivalent to the 100 minute testing time for oxazepam. Certain BZs may have blood concentration curves that have a more swift or gradual rise than other BZs (see Figure 15). Therefore, pre-peak testing times for different BZs may not always be directly comparable. Moreover, drug dose may also play a role in the ultimate peak blood concentration that is reached. Some doses may only be sufficient to produce explicit memory impairment but no implicit memory impairment at theoretical peak concentrations, because the peak for that dose is insufficient to cross the necessary threshold for inducing implicit memory impairment (see Figure 16). The results of Study 2 also indicate that BZ-induced explicit memory impairments may be more long lasting than implicit impairments, at least in the case of oxazepam (see Figure 14). However, BZs will need to be tested at even later time points than those used in Studies 2 and 3 to determine how long-lasting both implicit and explicit memory impairments are for various BZs with differing pharmacokinetic and pharmacodynamic properties.

Figure 15: A Visual Depiction of How Two Benzodiazepines Might Theoretically Have Different Implicit and Explicit Memory Impairment Profiles.

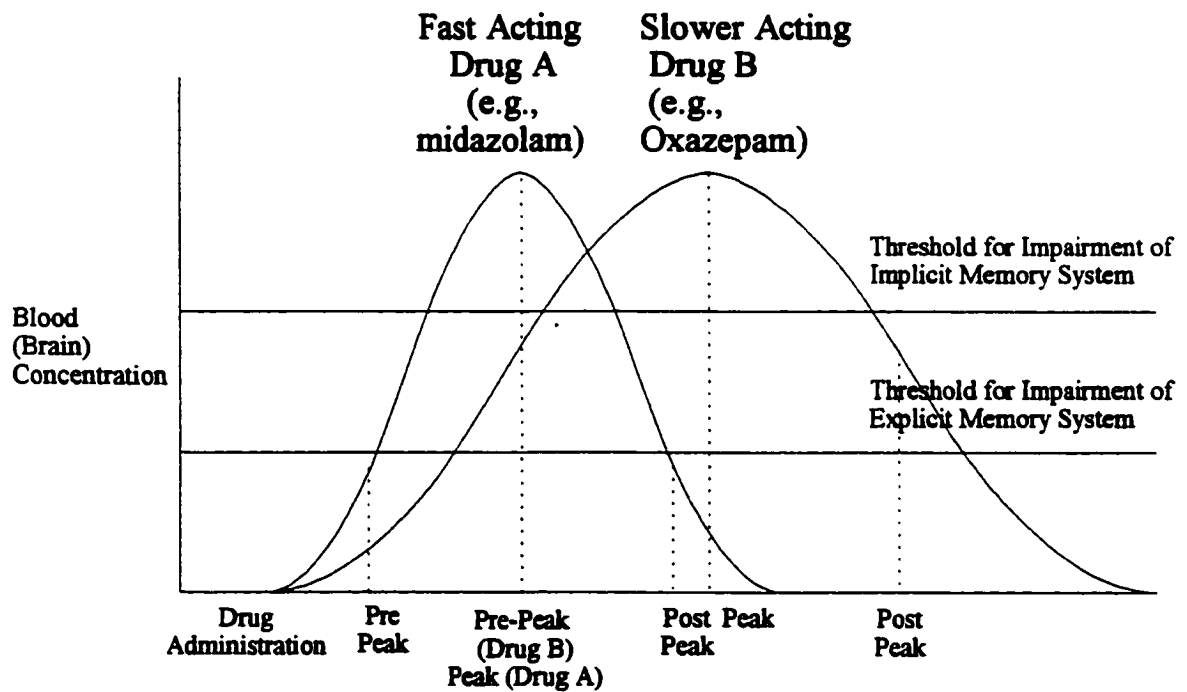
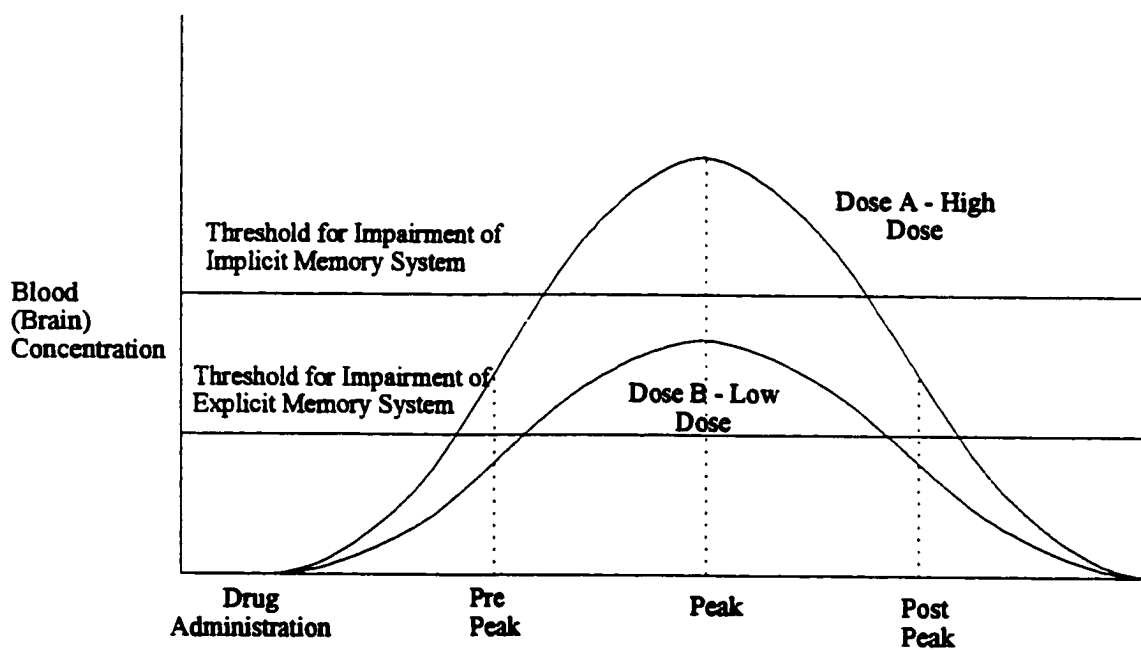


Figure 16: A Visual Depiction of How Two Doses of the Same Benzodiazepine Might Theoretically Have Different Implicit and Explicit Memory Impairment Profiles.



As was noted in the discussions of Studies 1 and 3, some researchers have suggested that an individual's responses on laboratory memory tasks (e.g., memory for word lists) may not reflect his/her memory performance in real-life situations (Curran, 1986). Certainly, individuals who are asked to remember a word list in a study may not be highly motivated to remember that list. In contrast, an individual who is studying for a test is most likely very motivated to remember the information encoded. In addition, real-world information to be encoded may be perceived as being more interesting than word lists which are presented in a lab. Therefore, it is possible that BZs do not impair memory in the real world, as long as individuals taking BZs are motivated to remember, or interested in the stimuli. In Study 1, participants watched a movie and were asked questions about the movie details at 15-minute time points. The results of this task indicated that BZ-treated participants had more difficulty than placebo-treated participants remembering the details of a movie. As Study 3 took place in a "real-world" situation, it was quite easy to design a memory task with presumably greater "ecological validity" than many lab-based memory tasks. Certainly, as the midazolam-treated children in Study 3 had difficulty remembering the details of their surgery day experience (specifically in the case of events that were likely to have occurred while they were under the influence of the drug), these findings suggest that BZ-induced amnesia occurs even for personally-experienced events that are highly salient. One advantage of the procedure used in Study 1 was that the specific memory testing times made it possible to examine the effects of BZs on explicit, episodic memory over time. The results indicated that the lorazepam-treated participants showed impaired memory at an earlier time point than the oxazepam-treated participants, lending further support to the idea that explicit memory

impairments do increase as the blood concentration of the BZ gets closer to peak levels, as was also suggested by the results of the cued recall task with the children in Study 3. In future studies of paediatric surgery, it would be interesting to ask children about recall of hospital experiences which occurred at specified time-points after drug administration to more closely determine the rate of episodic memory impairment over time. Peterson's (1999) methodology would be appropriate for this task, as she has also measured memory for hospital experiences. Peterson's methodology begins with a free recall question ("Tell me about when you went to the hospital. What happened?") and each category of hospital experiences is further probed with "Wh" questions ("Who was with you?"; "What color was the doctor's shirt?"). Observers who are with the child during the hospital visit are used to validate the accuracy of each memory. To further examine the time-dependence hypothesis in a future study, each category of hospital experiences would have to be timed to occur at a specified time post-drug (e.g., nursing tasks at ten minutes, surgery at forty minutes, wheelchair ride to day surgery at ninety minutes). As noted by Peterson (1999), it would be very important that children were not asked leading or "yes/no" questions about their surgery day experience. Studies indicate that preschoolers are very likely to answer "yes" to most "yes/no" questions, creating a response bias (Peterson, Dowden & Tobin, 1999). Peterson's probe questions ("Wh" questions) would serve as "cues" to remind children of specific target situations. This might make it less likely that children would simply say "I don't know", as many did in Study 3 when asked for their free recall of the entire surgery day. Also, this cued recall procedure elicits high levels of memory for hospital/injury events in children, even five years after the event (Peterson & Whalen, 2000).

Other Cognitive Effects of BZs

In my studies I also attempted to determine other cognitive effects of BZs and to what degree they might account for BZ-induced implicit and explicit “memory” impairments. Specifically, in each of my studies, sedation and attention were assessed at pre- and post-drug phases to determine how they were affected by BZ administration.

Overall, Studies 1 and 2 indicated that subjective sedation increases after administration of lorazepam or oxazepam. The results of Study 2 indicate that these subjective feelings of sedation are apparent prior to peak blood concentration of BZs, and remain relatively stable at the peak and post-peak testing time, at least in the case of oxazepam. It appears that increases in subjective sedation, like explicit memory impairments, occur early after drug ingestion and are relatively long lasting. Similarly, the use of objective sedation measures in Studies 2 and 3 indicated that participants exhibited impaired psychomotor speed at the pre-peak testing time, and these impairments remained stable at the peak and post-peak testing times across two drugs (oxazepam and midazolam). It should be noted that the Drug Group difference for objective sedation in Study 1 was not significant. However, the means were in the expected direction, and it is likely that the finding would have been significant if statistical power was increased (i.e., a larger number of participants). In Study 3, which used children as participants, an observer-rated sedation measure was used, as opposed to a subjective (child-rated) sedation measure. In contrast to findings with subjective and objective sedation measures, children were not rated as appearing sedated at the pre-peak testing time. Although this finding may simply reflect differences in the two BZs studied (oxazepam and midazolam), it is possible that individuals appear sedated at a later time

than they are aware of their own feelings of sedation or are affected by sedation on a psychomotor speed task. In the future, it would be interesting to use subjective, objective and observer-rated sedation scales in the same study, to examine further the possible time-dependent dissociation between the processes tapped by each type of sedation measure as suggested in Study 3.

A variety of attention tasks were used in Studies 1, 2, and 3 to assess the effects of lorazepam, oxazepam and midazolam on attention. Although I am well aware that attention cannot be assessed using a solitary test (VanZomeren & Brouwer, 1994), I was unable to examine the many components of attention that were described by Mirskey et al. (1991). As memory was my main focus in the current thesis, I was only able to examine the effects of BZs on focused attention and attentional encoding. In the future, it would be interesting to examine a number of attentional elements within the same study. In my thesis, Studies 1 and 3 used cancellation tasks that assess focused attention. Most previous studies have indicated that BZs impair performance on focused attention tasks (Bishop & Curran, 1995; Curran et al., 1991; Curran et al., 1993b). In Study 1, lorazepam impaired focused attention, as measured by a score created by combining time taken to complete the task with the number of omission errors on the task (cf. Bishop et al., 1996). In contrast, the oxazepam group had performance that fell between the lorazepam and placebo groups, and did not differ significantly from either group. It should be noted that the oxazepam group actually had performance that fell closer to that of the lorazepam group than the placebo group. Perhaps a study using more participants (i.e., increased statistical power) would have found a significant difference between the oxazepam and placebo-treated participants on focused attention.

As opposed to the adults in Study 1, the Study 3 children had commission errors, as well as omission errors on the focused attention task. This difference may indicate a developmental progression in performance on focused attention tasks. Thus, there is potential for the drug to exert different effects on this task in the different age groups by virtue of developmental differences in task performance. Alternatively, the differences in the errors noted in Study 1 and 3 could represent drug differences (oxazepam and lorazepam influence only omission errors vs. midazolam which influences both omission and commission errors). As omission and commission errors appear to measure different processes (Smith et al., 1981), they were not combined into a total attention measure in Study 3. Therefore, attentional time, omissions, and commissions were analyzed separately. The results indicated that time taken to complete the deletion task (the “attentional” measure most likely to be contaminated by sedation) was impaired by midazolam at the pre-peak and peak encoding times. However, omission errors were only increased by midazolam when tested at peak blood concentration, suggesting a time-dependent increase in focused attentional impairments. Finally, commission errors were most common for the midazolam-treated group tested at 5 minutes. Although this finding could suggest an early disinhibiting effect of midazolam, this group had a higher baseline level of commission errors, and this finding thus needs to be replicated.

In Study 2, an attention task was used which measured attentional encoding (Digit Forward vs. Digit Backwards). This task requires participants to mentally manipulate a list of numbers and say the list in a backwards order. Previous studies indicate that the component of attention tapped by this type of task (i.e., attentional encoding) is impaired by BZs (Curran et al., 1987a ; Fluck et al., 1998). The results of Study 2 indicated that

attentional encoding is significantly impaired by oxazepam at pre-peak, peak, and post-peak testing times, indicating that impairments in attentional encoding are relatively stable and long-lasting. Overall, the results of Studies 1, 2, and 3 indicate that BZs appear to impair both focused attention and attentional encoding (cf. Bishop & Curran, 1995; Curran et al., 1987a). Future research is needed to determine how BZs affect other attentional processes (such as sustained and shifting attention), and how time course of the drug in question influences BZ-induced impairments in various attentional processes.

As it is possible that BZ-induced impairments in implicit and explicit memory are actually secondary to the inattention and sedation described above, a series of ANCOVAs were conducted for each study. These analyses involved covarying out attention and sedation from significant memory effects. Overall, these ANCOVAs indicated that BZ-induced implicit memory impairments are not influenced by BZ-induced subjective sedation, objective sedation, or attentional impairments (Studies 1 and 2). In contrast, BZ-induced explicit memory impairments, as measured by both the cued recall, and the real world memory tasks, are somewhat reduced after accounting for BZ-induced sedation and inattention (Studies 1-3). However, all explicit memory effects remained significant or marginally-significant, indicating that although attention and sedation do have some contribution to BZ-induced performance impairments on explicit memory tasks, they are not entirely responsible for the observed drug group memory differences (cf. Bishop & Curran, 1995). Likewise, these findings are consistent with previous experimental cognitive psychology findings that attentional manipulations affect explicit memory performance, while leaving implicit memory intact (Rabinowitz et al, 1982). As has been mentioned previously, the fact that inattention and sedation contribute to BZ-

induced explicit memory impairments, but are not involved in BZ-induced priming impairments lends further support to the idea that implicit and explicit memory processes are dissociable (Roediger & McDermott, 1993).

Although the results of the ANCOVAs are consistent with previous studies, covariance can be a problematic procedure. As noted by Curran et al. (1991), analysis of covariance is based on the assumption that the relationship between the variate and the covariate is linear. Obviously this is not always the case (e.g., the inverted U-shaped relationship between anxiety and performance; Broadbent, 1958). In addition, the covariance procedure can be less reliable when the covariate is significantly related to the independent variable (Pedhazur, 1982). As drug group status in this thesis did affect sedation and attention, the covariance procedure used in the current study is quite artificial. Future studies should be designed to manipulate level of attention or sedation, in an attempt to determine how these factors influence implicit and explicit memory at each time point. In addition, studies using flumazenil, a BZ-receptor antagonist, are also helpful for studying BZ-induced amnesia, in the absence of inattention and sedation (Hommer et al., 1993). It would also be interesting to examine the effects of BZs and flumazenil at several Encoding Times (pre-peak, peak, and post-peak) in an attempt to determine how encoding time interacts with this antagonist. This would allow investigators to determine if sedation and attention begin to exert more influence on memory impairment as the plasma concentration of BZs begins to dissipate. For example, if sedation and attention have more influence on memory at the post-peak testing time, the administration of flumazenil would reverse the sedative and attentional

effects of a BZ, and would reduce the memory impairments. In contrast, at the peak testing time, sedation and inattention would be reversed with no effect on memory.

Limitations of Thesis

As with any line of research, there are limitations to the methodology of the studies contained in this thesis. Most of the major limitations of this thesis (i.e., switch from perceptual to conceptual priming task in Studies 1 and 2 vs. Study 3; reliance on covariance; failure to observe priming on implicit task in Study 3) have been discussed previously. In addition, some minor limitations, which were specific to only one study, have been discussed in previous chapters (e.g., different encoding instructions used at the various encoding times in Study 2). Another potential difficulty with the current series of studies is that the number of participants in each group was small (10 participants per group). Although these small numbers might have led to decreased power to observe true drug effects, it should be noted that BZs have very large magnitude effects on memory, attention and sedation. The robustness of BZ effects on these various aspects of cognition is attested to by the fact that significant drug group effects were usually apparent using only 10 participants. Another potential problem with small sample sizes is the increased probability that random assignment will not be sufficient to control for between-group differences on potentially confounding factors. However, in all three studies, statistical analysis was used to ensure that the small groups were equivalent on demographic and pre-drug cognitive measures. In one instance random assignment to drug groups was not successful in equating groups for pre-drug cognitive performance. In Study 3 the groups were not equivalent at baseline for the number of commission errors on the focused attention task, making interpretation of the findings with this

measure problematic. Another problem is that many statistical analyses were conducted using these small sample sizes. This increases the chance of obtaining significant effects by chance. In addition, I reported marginal results found throughout the thesis, further increasing the chance of Type I error.

An additional limitation of the current thesis is that actual blood concentrations of BZs were not measured in any of the studies due to cost/practical constraints. However, the time points chosen for the current studies were based on research that indicated that peak plasma concentrations occurred at these times for a given BZ and a given dose (see review by Greenblatt, 1981). These theoretical peak times are obtained under highly controlled circumstances (e.g., control of food eaten by participant, control of weight of participant, etc.). I attempted to be equally careful to control for as many factors as possible that might affect time to peak plasma concentrations across participants (weight of participants, food eaten by participants). However, one limitation in this thesis is that drugs were given as a pre-determined therapeutic dose (Studies 1 and 2) rather than on a dose per body weight. Thus, blood levels likely varied across participants in these two initial studies more than they would have if dose had been determined on a participant-by-participant basis (i.e., dose per kg). This latter limitation was amended in Study 3 (where doses of midazolam were weight adjusted, as is normal in anaesthetic situations with children). Unfortunately, I did not obtain individual participants' weights in Study 3. This oversight means that the doses of midazolam actually given to each group could not be calculated for ready comparison with other studies that have used fixed dose administration.

In addition, one might also ask why plasma concentrations are at all important, when we are more concerned about the effect of BZs in the brain. Obviously, it is not possible to obtain brain levels of a BZ in a laboratory-based study with humans. However, research indicates that the passage of BZs from the blood to the brain is extremely rapid, and the amount of BZ present in the brain is directly proportional to the amount of drug in the bloodstream (Arendt, Greenblatt, & De Jong, 1983).

Another limitation of this body of research is the possibility of implicit memory contamination of performance on the explicit memory task (Roediger & McDermott, 1993). This issue might be particularly important in the case of cued recall tests of explicit memory since presentation of a three-letter word stem might serve to perceptually prime the unintentional retrieval of the target word. Although the methodology used in the current thesis was designed to reduce the possibility of explicit contamination of the implicit task (e.g., implicit task presented before the explicit task in Studies 1-3; use of separate encoding time groups so that memory tasks were not repeated in Studies 1 and 2), no attempt was made to control for the reverse possibility (i.e., implicit memory contamination of explicit task). With respect to these cross-influence issues, an experimental methodology believed to separate implicit and explicit memory processes has been developed. This methodology is the Process Dissociation Procedure (PDP) developed by Jacoby (1991). In this technique, participants initially encode a word list. Next, half the participants are instructed to complete word stems with items from the encoding list. If they cannot think of an item from the encoding list, they are asked to produce any item that completes the word stem. Therefore, responding on this task might be the result of explicit or of implicit memory processes. The second group of

participants is told to complete the word stems only with items that were not in the study list. Therefore, if participants produce a word from the encoding list when they are trying not to, they are thought to be using implicit memory processes. Jacoby (1991) stated that explicit memory could not lead to an encoding word on this task because explicit recollection should lead to exclusion of that word. Therefore, if intrusion errors on the second task occur at above chance levels, this is said to be evidence of priming. Therefore, the number of target words completed on the second task is considered to be a pure measure of implicit memory. Also, subtracting the target words produced on the second task (where the participant uses incidental processes only) from the target words produced on the first task (both incidental and explicit processes) is thought to serve as a pure measure of explicit memory.

Although the PDP methodology has been rarely used in the BZ and memory literature, one recent study by Vidailhet et al. (1996) used the process to investigate the effects of clinical doses of diazepam and lorazepam on implicit and explicit memory. The time of memory encoding occurred at 50 minutes post-drug for diazepam and at 110 minutes post-drug for lorazepam (i.e., slightly “pre-peak” blood concentrations for each drug). The results using the PDP indicated that lorazepam impaired scores on “pure” measures of both explicit and implicit memory, while diazepam impaired scores on only the “pure” explicit memory measure. This result was taken as further evidence that only lorazepam impairs implicit memory (cf. Curran, 1986).

Although the PDP shows some promise for investigating BZ impairments on “uncontaminated” indices of implicit and explicit memory, it should be cautioned that difficulties with this procedure have been identified (e.g., Roediger & McDermott, 1993).

The procedure is based on the assumption that participants will only exclude items on the second task based on explicit memory of the item. However, it seems possible that a participant could unintentionally retrieve the word and then explicitly recognize it and exclude it. If participants are excluding words that are produced with implicit memory processes, the PDP will overestimate how much contamination from explicit memory occurs on an implicit memory task. More research is needed before the PDP can be recommended as a useful procedure for dissociating implicit and explicit memory processes in general, or in the context of BZ impairments in particular.

A final limitation of this thesis is that some have suggested that it may be difficult to maintain double-blind procedures in studies of BZs, as drug group status can often be determined by observing the participants (Gruenbaum, 1993). In addition, it has been argued that participants may also become aware of their drug group status due to the side-effects associated with BZs (Gruenbaum, 1993). To deal with this problem, I attempted to choose cognitive tasks that were very objective in their scoring procedures. In addition, anecdotal observation suggests that some participants that did not appear to be “drugged” were, in fact, BZ-treated participants. Likewise, some of the placebo-treated participants appeared drowsy due to the 8:00 am testing time for Studies 1 and 2. Therefore, determination of a participant’s drug group status by the experimenter was not a “sure thing”. In an attempt to check the efficacy of the double-blind procedure, Curran and associates (1993b) actually asked the participants and the experimenter to guess as to the drug group status to which the participant had been assigned. The results indicated that only half of the participants correctly guessed whether they had received a drug or

placebo and the experimenter was correct only 61% of the time. Future research should continue to include such checks of the double-blind manipulation.

The Importance of This Line of Research

Overall, the results of the present line of research suggest that BZs affect both implicit and explicit memory if concentrations of the drug have reached a certain threshold. For the doses of the particular BZs used in Studies 1 and 2, this threshold appears to have been reached around the time of peak blood concentration of the specific BZ being tested. As was reviewed in Chapter 2, researchers are interested in the effects of BZs on memory for a variety of reasons. The novel findings of this thesis have implications for each of these areas of interest. The reasons why the effects of BZs are studied and the implications of the present thesis are as follows:

- 1) **To determine what aspects of memory are affected by BZs, and how long lasting these effects are:** The present series of studies has serious implications when considering the day-to-day functioning of the many individuals who are taking BZs on a regular basis. Until recently, it was believed that priming remained intact after ingesting a BZ. Theoretically, one could argue that if only explicit memory was impaired, a person could use strategies to increase their ability to function with this specific memory deficit (e.g., writing to-be-remembered information in a day planner). However, priming is an ever-present function in our lives and underlies the ability to complete most tasks (Tulving & Schacter, 1990). Studies now indicate that priming is impaired by BZs, even after long-term (5-20 years) use (Gorenstein et al., 1994). The fact that priming is impaired by BZs has serious implications for the ability of regular BZ users to adequately function (Tulving & Schacter, 1990). In

addition, these implicit memory impairments appear to be relatively long-lasting as seen at the post-peak testing time in Study 2 (although they do appear to wane more quickly than explicit memory impairments). It should be noted that for p.r.n. users (i.e., those who use BZs on an as needed basis; see Westra & Stewart, 1998), the plasma concentration curves would be relatively similar to those described in this thesis. In regular BZ users, the concentration of a BZ in the bloodstream also decreases over the time since the last dose was taken. This fluctuation of plasma concentration levels is greater with BZs that have shorter elimination half-lives (Cowley et al., 1991). Generally, an inter-dose interval equal to the elimination half-life for a specific BZ will yield a fluctuation in plasma concentration of no more than 50% above or below the steady-state concentration (Greenblatt & Shader, 1985). Nonetheless, many BZ users take BZs in a p.r.n. manner (Westra & Stewart, in press), making the present results regarding time course potentially applicable to the way in which BZs are often used in the real world. Future studies are needed to examine the time-dependent effects of BZs in long-term users, since the present studies examined only single acute doses of BZ. It is possible that the BZ impairment curve for implicit and explicit memory may be altered or shortened in regular users due to changes in the BZ receptors. Also, in regularly scheduled chronic BZ users, when steady state of a BZ is reached, peaks and troughs of blood concentrations might be minimized, making the time dependence issues covered in this thesis potentially less relevant for this type of BZ user. However, these ideas have not yet been studied.

The results of my thesis also indicate that BZ-induced memory deficits occur even when the information to be remembered is more interesting, personally relevant, or

salient. The fact that BZ-induced memory impairments are not limited to traditional laboratory-based memory tasks gives further credence to the notion that regular users of BZs may have seriously impaired ability to function in their day-to-day lives. The fact that individuals with BZ-induced memory impairments may not be aware of these deficits (i.e., that they may lack metamemory) also has serious implications for regular BZ users (Bacon et al., 1998). If an individual is aware of his/her memory deficits, they would be more likely to engage in strategies to overcome or compensate for their memory impairments (e.g., rehearsal, chunking).

2) To determine if BZ-induced amnesia is similar to organic amnesia or dementia:

Organic Amnesia. It has been suggested that BZs might be effective for inducing a temporary amnesia, making it easier to study factors surrounding organic amnesia (Brown et al., 1982). However, based on the results of my thesis, it appears that BZ-induced memory deficits are not sufficient for the study of organic amnesia. Overall, the main diagnostic criterion of organic amnesia (e.g., Korsakoff's syndrome, anoxia, Herpes Simplex Encephalitis) is that long-term explicit memory is impaired. As with BZs, short-term memory is not impaired in individuals with organic amnesia (Parkin, 1987). However, in contrast to the findings of this thesis, studies indicate that implicit memory task performance of individuals with organic amnesia is statistically indistinguishable from control participants (Squire et al., 1987). Although there have been some studies which have found priming impairments as a result of organic amnesia (e.g., Ostergaard, 1994), these priming impairments (e.g., faster decay of primed memories) are not similar to the BZ-induced priming impairments found in my thesis. Overall, it appears that BZs are not a reliable pharmacological model of

organic amnesia if memory is tested at the peak plasma concentration of the drug. However, it is possible that at pre-peak or post-peak testing times the memory deficits associated with BZ administration would be similar to the deficits associated with organic amnesia. Future studies of implicit and explicit memory should compare the effects of BZs at each of the three encoding times with a group of individuals who have organic amnesia.

Alzheimer's Disease. As Alzheimer's Disease (AzD) is a progressive disorder, the effects of this disease on memory are studied separately from the organic amnesic disorders described above (Parkin, 1987). Again, explicit memory impairments are one of the diagnostic criteria for AzD (Kopelman & Corn, 1988). In contrast to organic amnesia and BZ-induced amnesia, short-term memory deficits are also characteristic of AzD (Miller, 1975). Studies examining implicit memory impairments in individuals with AzD are far from conclusive. Some studies indicate that word-stem completion is impaired by AzD (Keane et al., 1991; Ostergaard, 1994) while others suggest normal priming (Grosse, Wilson, & Fox, 1990). It is possible that these variable findings are a result of differing severity levels of AzD participants used in each study. AzD is a progressive disease, and the Keane and associates (1991) study may have used participants who were more demented than those in the Grosse et al. (1990) study. Overall, the fact that AzD is associated with deficits in short-term memory indicates some differences between the disorder and BZ-induced amnesia. However, further study of individuals with AzD at various points in the progression of the disease (e.g., early stage, late stage) is needed to determine the relationship between the progression of the disease and priming impairments, and to

determine whether the time-dependent BZ impairments in priming observed in this thesis might be applicable to understanding priming impairments that have been observed in AzD patients (e.g., Keane et al., 1991).

3) To determine if theoretically distinct memory processes are empirically separable:

Overall, the results of my thesis support the idea that implicit and explicit memory are empirically separable. Specifically, the results of Study 2 indicate that BZ-induced implicit and explicit memory impairments have different time courses. Overall, explicit memory impairments appear at pre-peak testing times, and are still present at post-peak. However, implicit memory impairments are not observable until a certain higher threshold of drug concentration is reached (i.e., close to peak plasma concentrations for the drugs and doses studied in this thesis). In addition, these implicit memory impairments appear to wane before the explicit impairments have dissipated. The fact that implicit and explicit memory impairments do not share the same impairment curve lends support to the hypothesis that implicit and explicit memory tasks are measuring two distinct memory processes. In addition, the fact that BZ-induced inattention and sedation contribute to BZ-induced explicit memory impairments, but do not contribute to BZ-induced priming impairments lends further support to the idea that implicit and explicit processes are dissociable (Roediger & McDermott, 1993). Further research is needed to determine the neural mechanisms that are underlying these memory processes. Researchers should examine factors such as BZ receptor occupancy to determine if implicit and explicit memory impairments occur at different levels of occupancy. In addition, BZs should be

further investigated as potential probes for separating conceptual and perceptual priming processes.

- 4) To determine how BZs taken concurrently with psychotherapy might effect the therapy process. The majority of individuals who are receiving psychological treatment for anxiety disorders are also taking an anxiolytic medication (Otto et al., 1999). Typically, these individuals are taking BZs (Otto et al., 1999). As noted by Curran (1991), BZ-induced explicit memory impairments may cause clients to forget what they had discussed during a therapy session. However, if implicit memory was not impaired by BZs, treatment might still be effective. For example, an individual who receives exposure therapy for a dog phobia might not remember exactly what occurred in their last therapy session. However, if they have implicit memory for the process, they might feel less nervous the next time they are in contact with a dog. However, the results of my thesis indicate that both explicit and implicit memory can be impaired by BZs when a certain threshold level of BZ has been reached. Therefore, it is likely that BZs would severely interfere with the therapeutic process. Overall, results do indicate that CBT in combination with simultaneous BZ therapy is not conducive to optimal therapeutic learning (see review by Westra & Stewart, 1998). However, most combined CBT + BZ outcome studies did not take into account the time-dependent effects of BZs in combination with therapy sessions or exposure exercises. Perhaps therapy or exposure sessions combined with pre-peak or post-peak BZ levels might lead to decreased anxiety with intact implicit memory. It is possible that this would be conducive to the therapy process. To test this hypothesis, it would be very interesting to administer BZs to clinically-anxious

individuals at several time points before individual or group therapy sessions for anxiety such that the therapy sessions occurred at pre-peak, peak, or post-peak blood levels of BZ. It would also be possible to study this effect in a university laboratory setting. For example, individuals with high public speaking anxiety could be recruited for a cognitive-behavioural group designed to reduce this anxiety.

Participants could be administered BZs at one of the three time points described above before each of the sessions. At the completion of the group, individuals would be asked to give a speech, and their anxiety levels could be monitored and compared to a placebo-treated group.

Although most studies of CBT and BZs have not considered the effect of time point, two studies examined the effect of peak and post-peak drug levels on exposure processes in the treatment of phobias. In the first study (Marks, Viswanathan, Lipsedge, & Gardiner, 1972) phobic individuals were administered diazepam at either 4 hours or 1 hour pre-exposure and compared to a placebo-treated group. Overall, the results indicated that the post-peak condition lead to the most improvement in phobias at the end of the exposure session, followed by the peak diazepam group. The placebo-treated participants showed the least improvement in this study. This finding is consistent with the idea that post-peak BZs in combination with exposure therapy might actually be beneficial to the exposure process. However, there are several problems with this study that make it difficult to conclude that BZs actually facilitate the exposure process. First, the placebo-treated participants were not BZ-naïve (many participants had used BZs previously). Therefore, these individuals probably detected the absence of drug feeling and may have become even more anxious than a

BZ-naïve group would have been. This is called a “reverse placebo” effect (Heatherton, Polivy & Herman, 1989). Secondly, the actual exposure sessions were two hours long. Therefore, the post-peak group most likely began the study at post-peak levels, followed by some exposure without the benefits of BZs. Similarly, the peak group was actually both a peak and a post-peak group. This makes it very difficult to compare the three groups and make conclusions about the specific processes facilitating exposure. Another difficulty with the Marks et al. (1972) study was that a crossover design was used with each participant attending two exposure sessions and being randomized to peak, post-peak or placebo at each session. Although the results for the first session are consistent with the overall results (post-peak > peak > placebo), the design of the study makes it impossible to look at the long-term effects of BZ therapy on the outcome of exposure. It is possible that BZ treated participants in this study would actually show increased anxiety during future exposure to their phobic items. As with the flight phobics treated with alprazolam in the Wilhelm and Roth (1997) study, the diazepam treated individuals in the Marks et al. (1972) study may not have intact memory for the exposure to the phobic object, leading to increased (or maintained) anxiety in the future rather than habituation.

In a second study designed to overcome the difficulty with the crossover design used in the Marks et al. (1972) study, participants were administered diazepam or placebo at one of two testing times (Hafner & Marks, 1976). The post-peak drug administration occurred at 3 ¼ hours before exposure and the peak administration occurred 15 minutes before exposure began. The exposure session lasted three hours, with the addition of a 30-minute break (total time 3.5 hours). After exposure there

was a marginal trend for the post-peak group to have the most initial improvement. Again, this is consistent with the time-dependent hypothesis in that post-peak participants are predicted to have greater improvement than the peak group. However, by the one-month and six-month follow-up sessions the three groups were indistinguishable. Again, there are several problems with this study that make it difficult to reach conclusions about the time-dependent effects of BZs on exposure processes. First, exposure took place in a group setting containing the three study groups. Therefore, the group as a whole regulated the pace of the exposure. Therefore, differential rates of progress for the three test groups could not be assessed. In addition, as noted for the Marks et al. (1971) study, the length of the exposure session and the timing of the drug administration make it impossible to actually call the groups peak and post-peak. For the participants in the peak group, exposure began when blood concentrations would have been at pre-peak levels (15 minutes post-drug) and progressed to waning levels by the end of the session (195 minutes post-drug). It is highly likely that the individuals in the post-peak group would no longer be under the influence of diazepam by the end of the exposure session (almost 7 hours after drug administration).

Overall, the results of these studies are inconclusive due to the major methodological flaws in each. In future studies, the effects of pre-peak, peak and post-peak BZ administration should be studied before exposure sessions which are no more than one hour in length. In addition, longer-acting BZs (such as diazepam) could be used to ensure that blood levels during the sessions remained relatively consistent for individuals assigned to peak and post-peak groups.

Concluding Remarks

Overall, the results of the present series of studies indicate that implicit memory is impaired by BZs if memory encoding occurs around the time of the peak blood concentration of the drug being tested. Also, these implicit memory impairments may begin to wane as post-peak blood levels of the drug are reached. Alternatively, explicit memory is impaired by BZs at pre-peak, peak and post-peak levels, and there is some evidence that explicit memory impairments increase in magnitude from pre-peak to peak blood levels of BZ. Although BZs also lead to increased sedation and inattention, these processes are not wholly responsible for the amnesic effects of BZs.

The fact that both implicit and explicit memory processes are impaired by BZs is important for both theoretical and clinical reasons. Theoretically, the fact that implicit and explicit memory impairments do not share the same impairment curve lends support to the hypothesis that implicit and explicit memory tasks are measuring two separable memory processes. Clinically, implicit and explicit memory impairments are likely to be quite debilitating for individuals who are taking BZs on a regular basis. Likewise, for individuals using BZs in combination with psychotherapy, the amnesia associated with BZ administration might interfere with obtaining an optimal therapy outcome. Finally, the BZ-associated amnesia might be helpful to anaesthetists at the time of initial anaesthetic administration. However, BZs are likely to cause a bottle-neck in the recovery room, and may lead to increased anxiety (or contribute to anxiety maintenance) during future anaesthetic inductions.

In the future, individuals who are studying BZs should always take the time-dependent effects of the drug into consideration whenever they are designing studies.

Specifically, the many clinical studies on the efficacy of combination psychotherapy and pharmacotherapy that do not take the time of BZ administration into account (relative to therapy sessions and/or in vivo exposure exercises) are difficult to interpret due to the variable amnesic effects of BZs that are related to the time course of the particular BZ in question.

Appendix A

Brief Mast

- | | | |
|--|-----|----|
| 1. Do you feel you are a normal drinker? | YES | NO |
| 2. Do friends or relatives think you are a normal drinker? | YES | NO |
| 3. Have you ever attended a meeting of Alcoholics Anonymous (AA)? | YES | NO |
| 4. Have you ever lost friends or girlfriends/boyfriends because of drinking? | YES | NO |
| 5. Have you ever gotten into trouble at work because of drinking? | YES | NO |
| 6. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking? | YES | NO |
| 7. Have you ever had the Delirium Tremens (DT's), severe shaking, heard voices, or seen things that were not there after heavy drinking? | YES | NO |
| 8. Have you ever gone to anyone for help about your drinking? | YES | NO |
| 9. Have you ever been hospitalized because of drinking? | YES | NO |
| 10. Have you ever been arrested for drunk driving or driving after drinking? | YES | NO |

Appendix B

1. On how many occasions do you normally consume alcohol?:

_____ Times per week

_____ Times per month (if less than once a week)

_____ Times per year (if less than once a month)

2. How many alcoholic beverages do you normally consume per drinking occasion?
(Note: One alcoholic beverage = one bottle of beer, or one small glass of wine, or one shot/mixed drink containing an ounce of hard liquor)

_____ Beverages per occasion

Benzodiazepine Study

PLEASE read the instructions carefully:

The following questions concern information about your involvement and abuse of drugs. Drug abuse refers to (1) the use of prescribed or "over-the-counter" drugs in excess of the directions and (2) any non-medical use of drugs. Carefully read each statement and decide whether your answer is Yes (Y), No (N), or not applicable (N/A). Then circle the appropriate response on the sheet provided. Please do not mark on the question sheet.

1. Have you used drugs other than those required for medical reasons ?
2. Have you abused prescription drugs ?
3. Do you abuse more than one drug at a time ?
4. Can you get through the week without using drugs (other than those required for medical reasons) ?
5. Are you always able to stop using drugs when you want to ?
6. Do you abuse drugs on a continuous basis ?
7. Do you try to limit your drug use to certain situations ?
8. Have you had "blackouts" or "flashbacks" as a result of drug use ?
9. Do you ever feel bad about your drug abuse ?
10. Does your spouse (or parents) ever complain about your involvement with drugs ?
11. Do your friends or relatives know or suspect that you abuse drugs ?
12. Has drug abuse ever created problems between you and your spouse (boyfriend/girlfriend) ?
13. Has any family member ever sought help for problems related to your drug use ?
14. Have you ever lost friends because of your use of drugs ?

Benzodiazepine Study

15. Have you ever neglected your family or missed work/school because of your drug use ?
16. Have you ever been in trouble at work because of drug abuse ?
17. Have you ever lost a job because of drug abuse ?
18. Have you gotten into fights when under the influence of drugs ?
19. Have you ever been arrested for unusual behaviour while under the influence of drugs ?
20. Have you ever been arrested for driving while under the influence of drugs ?
21. Have you engaged in illegal activities in order to obtain drugs ?
22. Have you ever been arrested for possession of illegal drugs ?
23. Have you ever experienced withdrawal symptoms as a result of heavy drug intake ?
24. Have you had medical problems as a result of your drug use (e.g. memory loss, hepatitis, convulsions, bleeding, etc.) ?
25. Have you ever gone to anyone for help for a drug-related problem ?
26. Have you ever been to a hospital for medical problems related to your drug use ?
27. Have you ever been involved in a treatment programme specifically related to drug use ?
28. Have you been treated as an out-patient for problems related to drug abuse ?

Appendix D

Logical memory Task

Administer both stories. Score 1 point for each correct item.

Story A

Anna/ Thompson/ of South/ Boston/
Employed/ as a cook/ in a school/ cafeteria/
Reported/ at the City Hall/ Station/ that she had been held up/
On State Street/ the night before/ and robbed/ of fifty-six dollars/
She had four/ small children/the rent was due/ and they had not eaten/
for two days/ The police/ touched by the woman's story/
took up a collection/ for her/

Total Score _____
(Max = 25)

Story B

Robert/ Miller/ was driving/ a ten-ton/ truck/
Down a highway/ at night/ in the Mississippi/ Delta/ carrying eggs/
To Nashville/ when his axle/ broke/ His truck skidded/
Off the road/ into a ditch/ He was thrown/ against the dashboard/
And was badly shaken/ There was no traffic/
and he doubted that help would come/ Just then his two-way radio/ buzzed/
He quickly answered/ "This is Grasshopper"/

Total Score _____
(Max = 25)

Appendix E

N E A P W B V L A Q H R Y A G M Z L A O D A
X Z R U W A T I S C N K O X A P Q V A
A F Z R U W A T I S C N K O X A P Q V A
Q I O B G A V K Y R D U P A A Z T F S J A L B R C
B A L P P A A E I J O L Z H V X Q A F W U A
T J S M F K A V K A H M A D P V A I B X
F N R E B A W C P J S Y A A C W I G A L
I A Z X O A L T Y G N P F A C W I G A L
U A Q D M W G E F A V L R A S B X M Q U R A H N
O K C H W G E F A V L R A S B X M Q U R A H N
Y D A H R I G F S A J S R D P H N R G O A E V
E W L A T M V I A K E X A F P
T A L A T M V I A K E X A F P
R H P Y N K A S B W L U I B J O A Z Q A T S Y
J S I A L K G C A E P R R P W U L D Q A T S Y
D A E N F A J R E K C H V A O G T B A
C Q T B A O R J M F B A A I M D S G A K F P C N
A L I D A F P Z V O R U E J Y A U U I D A
S E G D W F G A H T T K A C A M R Y

Appendix F

LARGE	red	<u>big</u>	silent	wet
(1) TALK	draw	eat	speak	sleep
(2) PERMIT	allow	sew	cut	drive
(3) PARDON	forgive	pound	divide	tell
(4) COUCH	pin	eraser	sofa	glass
(5) REMEMBER	swim	recall	number	defy
(6) TUMBLE	drink	dress	fall	think
(7) HIDEOUS	silvery	tilted	young	dreadful
(8) CORDIAL	swift	muddy	leafy	heartly
(9) EVIDENT	green	obvious	skeptical	afraid
(10) IMPOSTOR	conductor	officer	book	pretender
(11) MERIT	deserve	distrust	fight	separate
(12) FASCINATE	welcome	fix	stir	enchant
(13) INDICATE	defy	excite	signify	bicker
(14) IGNORANT	red	sharp	uninformed	precise
(15) FORTIFY	submerge	strengthen	vent	deaden
(16) RENOWN	length	head	fame	loyalty
(17) NARRATE	yield	buy	associate	tell
(18) MASSIVE	bright	large	speedy	low
(19) HILARITY	laughter	speed	grace	malice
(20) SMIRCHED	stolen	pointed	remade	soiled
(21) SQUANDER	lease	belittle	cut	waste
(22) CAPTION	drum	ball	heading	ape
(23) FACILITATE	help	turn	strip	bewilder
(24) JOCOSE	humorous	paltry	fervid	plain
(25) APPRISE	reduce	strew	inform	delight
(26) RUE	eat	lament	dominate	cure
(27) DENIZEN	senator	inhabitant	fish	atom
(28) DIVEST	dispossess	intrude	rally	pledge
(29) AMULET	charm	orphan	dingo	pond
(30) INEXORABLE	untidy	involitile	rigid	sparse
(31) SERRATED	dried	notched	armed	blunt
(32) LISSOM	moldy	loose	supple	convex
(33) MOLLIFY	initiate	direct	pertain	abuse
(34) PLAGERIZE	appropriate	intend	revoke	maintain
(35) ORIFICE	brush	hole	building	lute
(36) QUERULOUS	maniacal	curious	devout	complaining
(37) PARIAH	outcast	priest	lentil	locker
(38) ABET	waken	ensue	incite	placate
(39) TEMERITY	rashness	timidity	desire	kindness
(40) PRISTINE	vain	sound	first	level

Benzodiazepine Study

Self-Rating of Sedation

Pre
 Post

Name: _____

PLEASE indicate how you feel at this moment by placing a mark along each line.

Alert _____ Drowsy

Excited _____ Calm

Clear-Headed _____ Fuzzy

Energetic _____ Lethargic

Quick _____ Slow

Finger Tapping Test

PRE
 POST

Name : _____

Instructions: "Now we are going to see how fast you can tap. We will use this little key here (point). Place your arm and hand in a comfortable position like this, and without moving your wrist or arm, I want you to tap as fast as you can with your forefinger like this (demonstrate). You will have to remember to let the key come all the way up and push it all the way down to click each time, or else the number on the dial won't change (demonstrate). Now move the board to a comfortable position for your (dominant) hand, and try it for practice (practice). I will tell you when to begin and stop each time. Remember to tap as fast as you can. Ready. Go."

TRIAL*	RIGHT	LEFT
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
AVERAGE		

Dominant Hand

Left
 Right

* 5 Trials or Until 5 Trials with Range < 5

Appendix I

Movie Memory Questions

Section 1

1. What year did the Hudson Bay Company relinquish its land to the North West?
2. What is a Metis?
3. What colour is Louis Riel's jacket?
4. What happened to the Metis who lost the arm wrestling match?
5. What religion is Louis Riel?

(Stop movie when we see Riel by a river)

Section 2

1. What is Mrs. Schulz buying for the Governor's reception?
2. How many people were with Riel at his father's gravesite?
3. What were the British-Canadians trying to do on the Metis land?
4. What skill does Riel have that most of the Metis don't?
5. Where is Mrs. Schulz's husband, the doctor, staying?

(Stop movie when Riel says "get the paper and pens!")

Section 3

1. What flag were the Canadians flying when they were arriving in Red River?
2. What month is it when Governor MacDougal arrives in Red River?
3. What game does John A. MacDonald play in this scene?
4. What does Gabrielle shoot out of the air?
5. What is Riel doing when the Canadians shoot at him?

(Stop when Riel lies on the ground)

Section 4

1. How much time are the British-Canadians given to get out of the house before they will be shot?
2. Who holds a gun to Riel's head?
3. Where was the trial of Thomas Scott?
4. What is Thomas Scott accused of?
5. What is Riel doing as Scott is shot?

(Stop after Thomas Scott is shot)

Section 5

1. What is the name of the new province?
2. What do Donald and Sir. John A. MacDonald toast to?
3. What colour are the peacekeeper's jackets?
4. What did the poster say that the Metis man nailed to the house?
5. What was the weather like during the shoot-out?

(Stop when Sir John A. MacDonald says "go home")

Appendix I (Continued)

Section 6

1. Why did Riel laugh out loud during the church service?
2. Where did Riel's friends send him so he could hide?
3. What was in the tea that Riel drank at that asylum?
4. When Gabrielle was talking to the reporter, what did the sign behind them say?
5. What kind of plant does the Bishop show Sir John A. MacDonald?

(Stop at Riel's arrival in Saskatchewan)

Section 7

1. What is Sir John A. MacDonald's toy train doing that makes him laugh?
2. What did Riel suggest the Metis might do in his letter to Sir John A. MacDonald?
3. Which side fired the first shot in the battle?
4. Where is Gabrielle shot?
5. What happens when Louis prays for Gabrielle to get better?

(Stop when we see the large gun on the train)

Section 8

1. What is special about the gun the Americans show the Canadians?
2. What does the soldier shoot with the gun while showing it to the Canadians?
3. How many people were at the meeting with Sir John A. MacDonald (excluding Sir John)?
4. What is Riel doing during the gun fight between the Metis and the soldiers?
5. What do the Metis use to make bullets?

(Stop when the Church is boarded up with the priest inside)

Section 9

1. What is the first weapon to be fired during the battle?
2. What do the Metis steal from the bodies of the soldiers?
3. What do the Metis burn at the end of the fight?
4. How many people did Riel shoot during the battle?
5. What does Riel do in the woods after losing the battle?

(Stop when Gabrielle says "that was the last time I saw him")

Section 10

1. What was Riel charged with?
2. What did Riel's lawyers plead for him?
3. In what month was Riel hanged?
4. What was the priest saying as they put the noose on Riel's neck?
5. What did Riel tell Father Richard before he was hung?

Appendix J

Encoding Word Lists

List 1a

Snore
Achieve
Mock
Emerald
Protect
Vast
Chill
Section
Jolt
Ride
Time
Cord
Coffin
Insight
Committee
Slender
Soft
Group
Lame
Paradise
Sufficient
Humid
Tennis

List 2a

Shell
Filler
Blend
Force
Spider
Report
Honour
Useless
Gray
Gentle
Sport
Serious
Fool
Market
Town
Devote
Holy
Hazy
Happen
Tear
Trace
Sneeze
Celebration

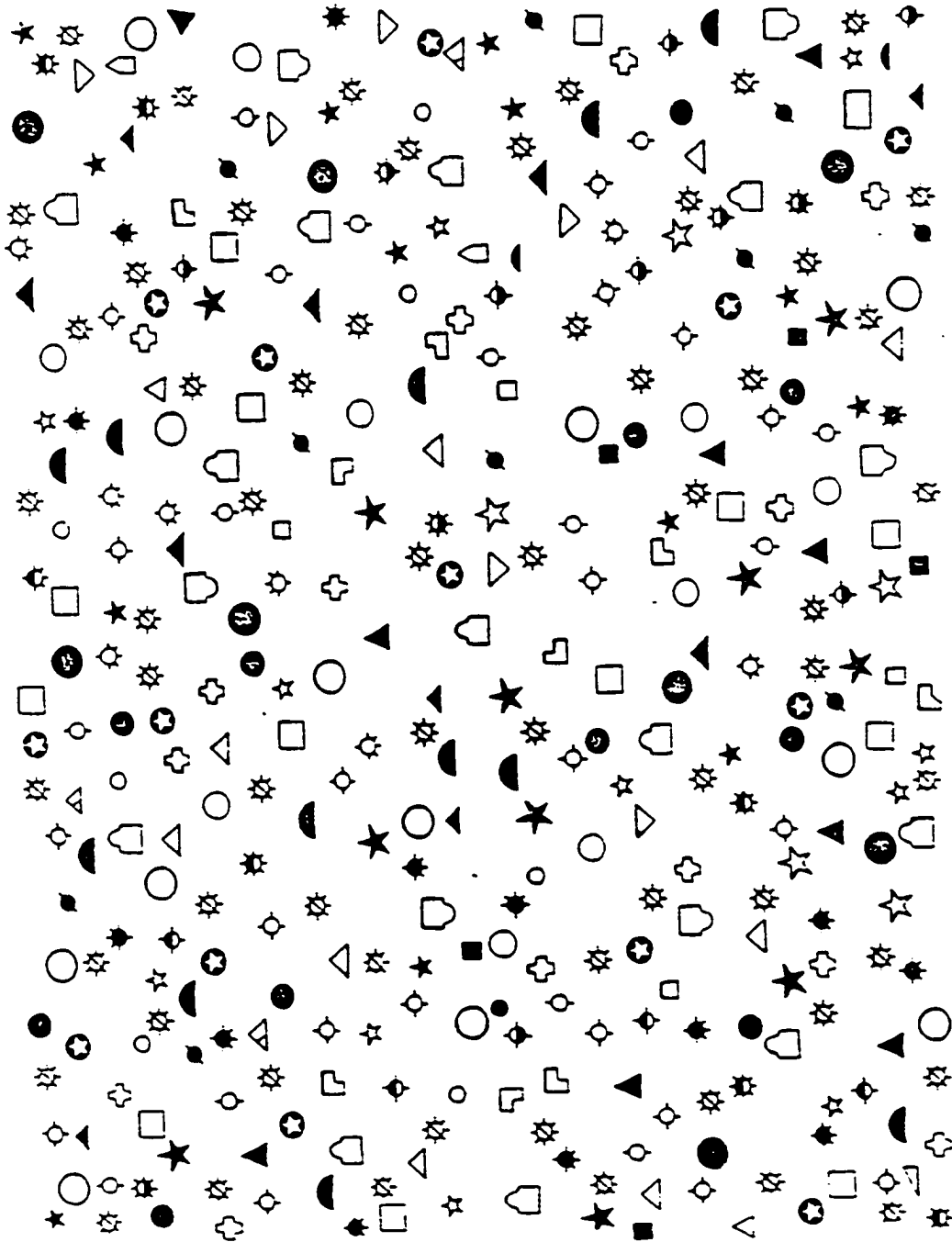
List 1b

Tremble
Pride
Lonely
Capable
Hatch
Clam
Office
Lousy
Station
Lease
Demon
First
Approve
Indicate
Accept
Final
Banana
Decorate
Further
Attend
Warrior
Prepare
Border

List 2b

Imperfect
Morning
Category
Fragile
Poise
Illusion
Excite
Peace
Plate
Mutation
Unsafe
Silent
Tingle
Crane
Inert
Include
Injure
Embrace
Tumour
Cereal
Supply
Host
Miracle

Appendix K



Appendix L

Encoding Ratings

-2	-1	0	+1	+2
Not at All		Indifferent		Very Much

Appendix M

10. DIGIT SYMBOL

1	2	3	4	5	6	7	8	9	SCOPE
—	⊥	≡	∟	∪	○	∧	×	≡	□

SAMPLES																								
2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4
1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3
6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7
9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

Appendix N

BRE _____
DRA _____
CHE _____
PAT _____
BRO _____
NEG _____
OVE _____
REJ _____
FRI _____
PER _____
CAL _____
MIS _____
DIS _____
STR _____
HAR _____
PLE _____
LET _____
ADV _____
FAT _____
GAR _____
SEI _____
HEA _____
ABO _____
ANC _____
VIO _____
DES _____
INF _____
DEF _____
PHY _____
HOP _____
ASH _____
ASS _____
SWE _____
PIL _____
WIN _____
IDE _____
ENT _____
SWI _____
BUT _____
MIL _____
FAI _____
CAR _____
WOU _____
CHO _____
REL _____
WEA _____

Appendix O

DEP _____
PAI _____
MER _____
EXP _____
SAL _____
HER _____
COL _____
MAN _____
HEL _____
DEL _____
ERR _____
OCC _____
INT _____
ROB _____
DEA _____
INA _____
RAI _____
SHA _____
RET _____
CRI _____
DAT _____
MOD _____
AMB _____

Benzodiazepine Study

Digit Span Test - WAIS-R

Name: _____

Forwards

Instructions: "I am going to say some numbers. Listen carefully, and when I am through say them right after me."

	Trial 1	P/F	Trial 2	P/F
Item				
1	582		694	
2	6439		7286	
3	42731		75836	
4	619473		392487	
5	5917428		4179386	
6	58192647		38295174	
7	275862584		713942568	

Backwards

Instructions: "Now I am going to say some more numbers, but this time when I stop I want you to say them backwards. For example, if I say 7-1-9, what would you say? [subject's response]."

	Trial 1	P/F	Trial 2	P/F
Item				
1	24		58	
2	629		415	
3	3279		4968	
4	15286		61843	
5	539418		724856	
6	8129365		4739128	
7	94376258		72819653	

(NOTE: Give both trials. Scoring: 2 points if subject passes both trials, 1 point if subject passes only 1 trial, and 0 if both trials are failed. Discontinue after failure on both trials of any item).

Modified Yale Preoperative Anxiety Scale (mYPAS)

- A. Activity
- B. Vocalizations
- C. Emotional Expressivity
- D. State of Arousal
- E. Use of Parent
- F. Overall Child Anxiety Level

A. Activity

- 0. Can't code (child not visible)
- 1. Looking around, curious, playing with toys, reading (or other age appropriate behavior); moves around holding area/treatment room to get toys or go to parent; may move toward OR equipment
- 2. Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality
- 3. Moving from toy to parent in unfocused manner, nonactivity derived movements; frenetic/frenzied movement or play; squirming, moving on table, may push mask away or clinging to parent
- 4. Actively trying to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or will not separate from parent, desperate clinging
- 9. Uncertain

B. Vocalizations

- 0. Can't code (child not visible or can't hear audio)
- 1. Reading (nonvocalizing appropriate to activity), asking questions, making comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond
- 2. Responding to adults but whispers, "baby talk", only head nodding
- 3. Quiet, no sounds or responses to adults
- 4. Whimpering, moaning, groaning, silently crying
- 5. Crying or may be screaming "no"
- 6. Crying, screaming loudly, sustained (audible through mask)
- 9. Uncertain

C. Emotional Expressivity

- 0. Can't code (can't see face or child not visible)
- 1. Manifestly happy, smiling, or concentrating on play
- 2. Neutral, no visible expression on face
- 3. Worried (sad) to frightened, sad, worried, or tearful eyes
- 4. Distressed, crying, extreme upset, may have wide eyes
- 9. Uncertain

D. State of Apparent Arousal

- 0. Can't Code (child not visible)
- 1. Alert, looks around occasionally, notices watches what anesthesiologist does with him/her (could be relaxed)
- 2. Withdrawn child sitting still and quiet, may be sucking on thumb or face turned into adult
- 3. Vigilant looking quickly all around, may startle to sounds, eyes wide, body tense
- 4. Panicked whimpering, may be crying or pushing others away, turns away
- 9. Uncertain

E. Use of Parents

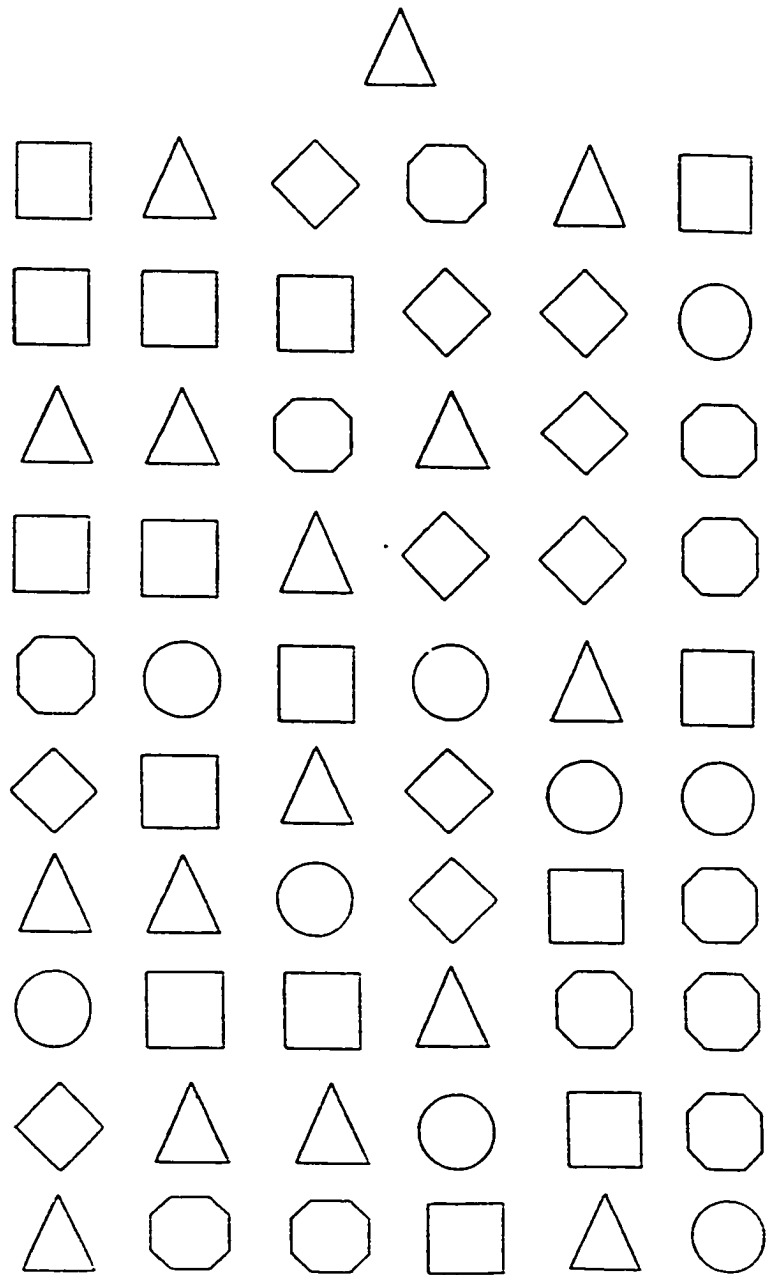
- 0. Can't code (child not visible)
- 1. Busy playing, sitting idle, or engaged in age appropriate behavior and doesn't need parent; may interact with parent if parent initiates the interaction
- 2. Reaches out to parent (approaches parent and speaks to otherwise silent parent), seeks and accepts comfort, may lean against parent
- 3. Looks to parents quietly, apparently watches actions, doesn't seek contact or comfort, accepts if offered or clings to parent
- 4. Keeps parent at distance or may actively withdraw from parent, may push parent away or desperately clinging to parent and will not let parent go
- 9. Uncertain

Appendix R

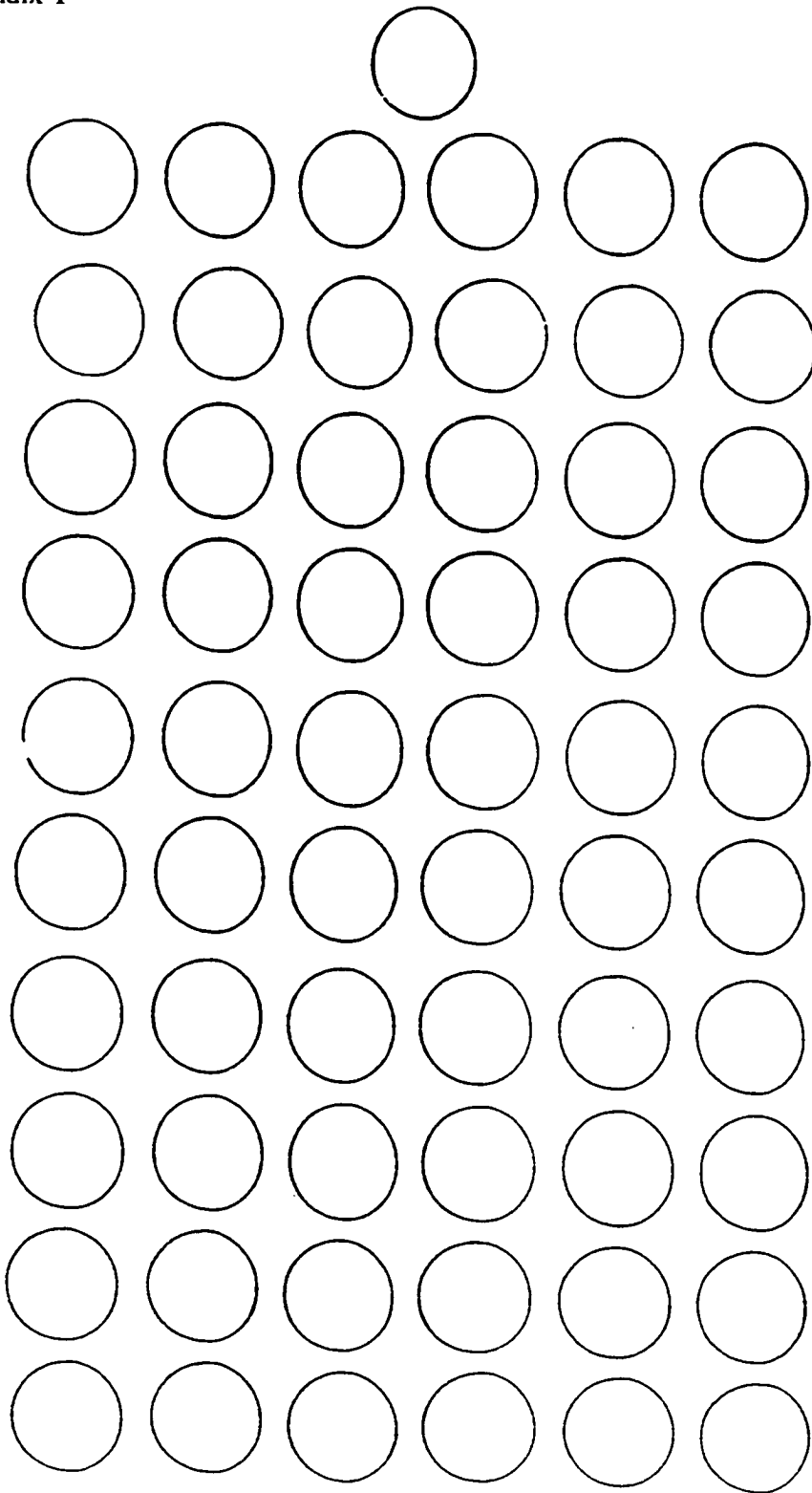
Jim was a boy whose best friend was Pepper. Pepper was a big black dog. Jim liked to walk in the woods and climb the trees. Near Jim's house was a very tall oak tree with branches so high that he couldn't reach them. Jim always wanted to climb that tree, so one day he got a ladder from home and carried it to the oak tree. He climbed up, sat on a branch, and looked out over his neighborhood. When he started to get down, his foot slipped, his shoe fell off, and the ladder fell to the ground. Jim held onto a branch so he didn't fall, but he couldn't get down. Pepper sat below the tree and barked. Suddenly Pepper took Jim's shoe in his mouth and ran away. Jim felt sad. Didn't his friend want to stay with him when he was in trouble? Pepper took the shoe to Anna, Jim's sister. He barked and barked. Finally Anna understood that Jim was in trouble. She followed Pepper to the tree where Jim was stuck. Anna put the ladder up and rescued Jim. Wasn't Pepper a smart dog?

Free Recall	Free Recall Score	Cued Recall Questions	Cued Recall Score	Item Score
1 Jim	2 0	1 What was the boy's name?	1 0	0 1 2
2 Pepper	2 0	2 What was the dog's name?	1 0	0 1 2
3 big	2 0	3 What size was the dog?	1 0	0 1 2
4 black	2 0	4 What color was the dog?	1 0	0 1 2
5 liked to walk in the woods or climb trees	2 0	5 What did Jim like to do for fun?	1 0	0 1 2
6 tree/oak with branches too high for Jim to reach	2 0	6 What was near Jim's house?	1 0	0 1 2
7 climbed the tree/oak	2 0	7 What did Jim do one day?	1 0	0 1 2
8 got a ladder or carried a ladder to the tree/oak	2 0	8 How did Jim get up in the tree/oak?	1 0	0 1 2
9 looked out over the neighborhood or looked around	2 0	9 What did Jim do when he got up in the tree/oak?	1 0	0 1 2
10 slipped or shoe fell or ladder fell or got stuck or couldn't get down	2 0	10 What happened when Jim started to get down?	1 0	0 1 2
11 Pepper ran for help or went to get help or ran away	2 0	11 What did Pepper do when Jim got stuck?	1 0	0 1 2
12 Jim was sad or thought Pepper didn't want to stay	2 0	12 How did Jim feel when Pepper ran away?	1 0	0 1 2
13 Anna	2 0	13 What was the girl's name?	1 0	0 1 2
14 Jim's sister	2 0	14 Who was Anna?	1 0	0 1 2
15 took her Jim's shoe	2 0	15 How did Pepper get Anna to understand that Jim was in trouble?	1 0	0 1 2
16 barked and barked	2 0	16 What else did he do? or, if used item 15 as cue: What did Pepper do after he took the shoe to Anna?	1 0	0 1 2
17 Anna put the ladder back up or rescued Jim or helped Jim	2 0	17 What did Anna do after she realized that Jim was in trouble?	1 0	0 1 2

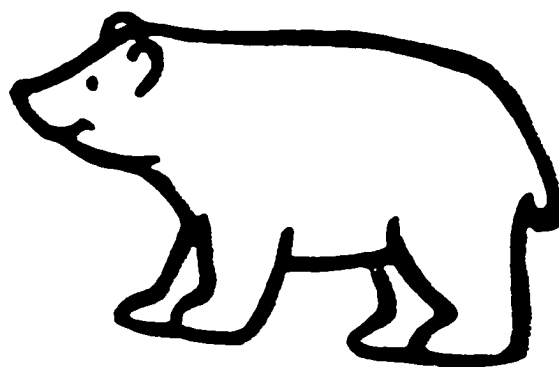
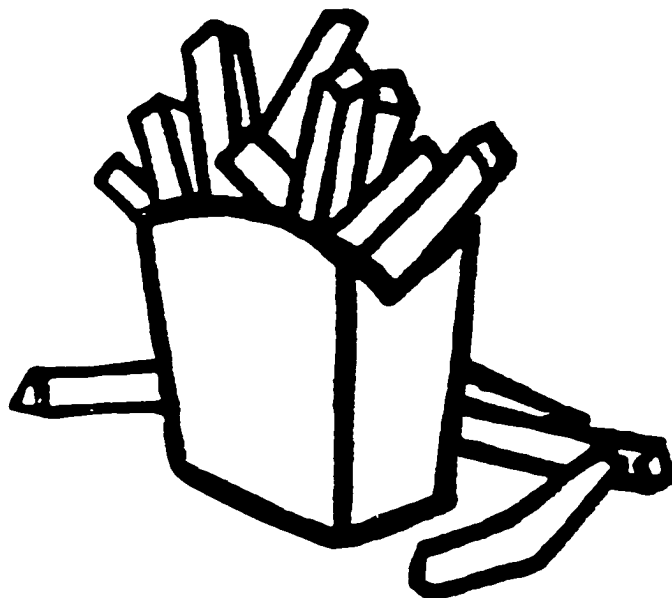
Appendix S



Appendix T



Appendix U



Appendix W

Implicit Memory Stories

- A. Now I'm going to tell you a story about another little (boy/girl) your age named (Joshua/Emma). Every Sunday afternoon (Joshua/Emma's) grandmother takes (Joshua/Emma) and all (his/her) brothers and sisters to the neighborhood park. (Joshua/Emma) loves to go to the park because there's so much you can do there. You can run around and play or you can sit in the fresh air and just look around. When (Joshua/Emma) goes to the park, what do you think (he/she) sees? Tell me everything you think (he/she) sees in the park.
- B. Now I'm going to tell you a story about another little (boy/girl) your age named (Daniel/Kathleen). Every summer (Daniel/Kathleen's) aunt takes (Daniel/Kathleen) and all (his/her) friends to the zoo. (Daniel/Kathleen) loves going to the zoo because there's so much to see there. (He/She) loves looking at all the animals in the zoo. When (Daniel/Kathleen) goes to the zoo, what do you think (he/she) sees? Tell me everything you think (he/she) sees at the zoo.
- C. Now I'm going to tell you a story about another little (boy/girl) your age named (Bill/Sarah). Every weekend (Bill/Sarah's) mother takes (Bill/Sarah) to a restaurant. (Bill/Sarah) loves going to the restaurant because there is so much to do and see there. (Bill/Sarah) loves looking at everything in the restaurant. When (Bill/Sarah) goes to the restaurant, what do you think (he/she) sees? Tell me everything you think (he/she) sees at the restaurant.
- D. Now I'm going to tell you a story about another little (boy/girl) your age named (Rob/Krista). Every night (Rob/Krista) likes to help her parents make supper in the kitchen. (Rob/Krista) loves helping in the kitchen because there's so much to see there. There's neat stuff to look at everywhere in the kitchen. When (Rob/Krista) is in the kitchen, what do you think (he/she) sees? Tell me everything you think (he/she) sees in the kitchen.

Explicit Task

Place pictures face down in front of child. "These are the pictures that I showed you earlier"

Pre-Surgery: A (park) B (zoo) C (restaurant) D (kitchen)

Pre-Surgery: Can you name the pictures I showed you of things you see at the park/zoo/restaurant/kitchen?

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

Post-Surgery: A (park) B (zoo) C (restaurant) D (kitchen)

Post-Surgery: Can you name the pictures I showed you of things you see at the park/zoo/restaurant/kitchen?

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

Prompt (if child does not spontaneously mention six) -What other pictures did I show you of things you see in a ____?

Keep prompting until six items are mentioned or until child states that they cannot think of any more.

Appendix Y

Memory for Surgery

Can you tell me about what happened today since you came to the hospital?

Child can be given up to three prompts:

What else happened?

What happened after that?

Then what?

If child says "I don't know" experimenter says "well first you arrived here with your mother/father and met me. What happened next?"

Appendix Z

Now I'd like to ask some questions about specific behaviors that may or may not change following a hospital experience.

1=Much less than before 2=Less than before 3=Same as before 4=More than before 5=Much more than before

1. Does your child make a fuss about going to bed at night? -----1 2 3 4 5
2. Does your child make a fuss about eating? -----1 2 3 4 5
3. Does your child spend time just sitting or lying and doing nothing? -----1 2 3 4 5
4. Does your child need a pacifier? -----1 2 3 4 5
5. Does your child seem to be afraid of leaving the house with you? -----1 2 3 4 5
6. Is your child uninterested in what goes on around him (or her)? -----1 2 3 4 5
7. Does your child wet the bed at night? -----1 2 3 4 5
8. Does your child bite his (or her) finger nails? -----1 2 3 4 5
9. Does your child get upset when you leave him (or her) alone for
a few minutes? -----1 2 3 4 5
10. Does your child need a lot of help doing things? -----1 2 3 4 5
11. Is it difficult to get your child interested in doing things (like playing
games with toys)? -----1 2 3 4 5
12. Does your child seem to avoid or be afraid of new things? -----1 2 3 4 5
13. Does your child have difficulty making up his (or her) mind? -----1 2 3 4 5
14. Does your child have temper tantrums? -----1 2 3 4 5
15. Is it difficult to get your child to talk to you? -----1 2 3 4 5
16. Does your child seem to get upset when someone mentions doctors or
hospitals? -----1 2 3 4 5
17. Does your child follow you everywhere around the house? -----1 2 3 4 5
18. Does your child spend time trying to get or hold your attention? -----1 2 3 4 5
19. Is your child afraid of the dark? -----1 2 3 4 5
20. Does your child have bad dreams at night or wake up and cry? -----1 2 3 4 5
21. Does your child have irregular in bowel movements? -----1 2 3 4 5
22. Does your child have trouble getting to sleep at night? -----1 2 3 4 5
23. Does your child seem to be shy around strangers? -----1 2 3 4 5
24. Does your child have a poor appetite? -----1 2 3 4 5
25. Does your child tend to disobey you? -----1 2 3 4 5
26. Does your child break toys or other objects? -----1 2 3 4 5
27. Does your child suck his (or her) fingers or thumbs? -----1 2 3 4 5

Appendix AA

Encoding Categories

Not Under the Influence: Child scores 1 point for each category named (only one point per category).

Category	Examples
Registration	"I got my arm band" "I got registered"
Cognitive Tasks (excluding memory tasks)	"I played with a bingo marker" "You told me to remember a story" "I played games"
Describing the Day Surgery Room/Bed	"I was in the room with the curtain"
Pajamas	"I got my striped pajamas on"
Post-Recovery	"I ate a Popsicle" "I rode in a wheelchair"
Negative After Surgery Events	"I threw up" "It hurt" "I cried" "I felt dizzy"
Nursing Tasks	"The lady checked my blood" "I took my medicine" "She put a red thing on my finger"
Day Surgery Surroundings (main area)	"I saw the tiger balloon"
Other Activities	"I watched a movie" "I read a book" "I played with toys"
Information about the Examiner	"I met Susan" "You put on a funny hat"

Under the Influence (most likely): Child scores 1 point for each category named (only one point per category. Child does not score points for saying "I got my tubes in" or "I slept").

Category	Examples
Traveling in the Bed	"I went down the aisle" "I rode in the bed"
Entering the Operating Room	"I went in the new room"
Operating Room Environment	"I saw a big light on the ceiling"
Getting Anaesthetic	"They put a mask on my face" "I breathed stinky air" "I held the mask on my face"
Memory Task	"You showed me a picture of a bunny"

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