DISSERTATION

PREDICTORS OF PRESCRIBED AND UNPRESCRIBED METHYLPHENIDATE ABUSE

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY JOSEPH P. MCMONAGLE ENTITLED PREDICTORS OF PRESCRIBED AND UNPRESCRIBED ADOLESCENT METHYLPHENIDATE ABUSE BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

PREDICTORS OF PRESCRIBED AND UNPRESCRIBED METHYLPHENIDATE ABUSE

This study used self-report survey data from students (grades 9 through 12) from a nationally derived sample (n=17,000) to explore hypothetical predictors of Methylphenidate (MPH) abuse for youths with and without a MPH prescription history. Variables included; history of MPH prescription, general level ('style') of substance abuse, types of aggression, gender, smoking, and the interaction of MPH prescription history and smoking.

6.4% of the sample were found to have abused MPH during the last year. There were no significant age group differences for MPH abuse. Also, MPH prescription alone did not predict MPH abuse. However, multiple regression showed that after 'style', the interaction between a history of MPH prescription and smoking behaviors was the next most significant predictor. After that, smoking and physical assault on a person were also somewhat significant.

A three group (prescribed/abusing, prescribed/non-abusing, and non-prescribed/abusing) discriminant analysis showed that it was possible to discriminate between the three groups using most of these predictor variables. While non-abusers were the 'most different' group, particularly in relation to their general drug use and smoking behaviors, it was also shown that the prescribed/abusing group was different from the non-prescribed/abusing group by being more likely to be male and aggressive.

A discussion of the role of nicotine as a significant predictor of MPH abuse, and its particular importance for those with a history of MPH prescription was included.

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Predictors of Prescribed and Unprescribed Adolescent Methylphenidate Abuse

CHAPTER I

INTRODUCTION

The purpose of this study is to conduct a preliminary and exploratory investigation of factors that predict the abuse of the prescription drug methylphenidate in an adolescent population. This kind of study has not been done up to the present time. This study should go some way to assisting in the identification of risk factors such as aggression, gender, previous exposure to prescribed methylphenidate, and the use of other substances (including nicotine) as part of future preventative strategies.

Synthesized in 1944 and used initially as an analeptic for barbiturate overdose Methylphenidate (MPH) or Ritalin is the most commonly physician prescribed stimulant medication in the United States (Safer & Zito, 2000). MPH comes in various forms. MPH 5, 10, and 20mg immediate release tablets are marketed by Novartis Corporation as Ritalin®. Generic products are also available. Therapeutic doses normally range from 10 to 60 mg. MPH is rapidly and completely absorbed. Onset of action is rapid and lasts about 1 to 4 hours. Half life is short at about 1 to 3 hours. Sustained release tablets like Ritalin-SR and others (at 20mg) are longer lasting but onset is slower and peak serum levels are lower. Extended release tablets (Concerta 18, 36, and 54mg among others) maintain similar serum concentrations to multiple administration immediate release MPH. MPH's mechanism of action is not completely understood but involves multiple neurotransmitters including dopamine, norepinepherine, and serotonin. Behavioral effects are believed to be mostly mediated by dopaminergic effects (Klein-Schwartz, 2002).

MPH is used for a variety of disorders including narcolepsy, Tourette's syndrome, depression, and traumatic brain injury (Klein-Schwartz & McGrath, 2003). But its most widespread use is as a psychotherapeutic agent in the treatment of Attention Deficit Hyperactivity Disorder. ADHD is diagnosed in 3-5% of school-age children, with diagnosis centering on two major symptoms: (1) inattention and (2) hyperactive-impulsive behavior (or disinhibition) (Barkley, 1997). While most individuals suffer both symptoms, some do not. Therefore, ADHD is further sub-typed based upon the predominant symptom pattern for the last 6 months. These sub-types are defined as Predominantly Hyperactive-Impulsive; Predominantly Inattentive; and Combined types. Diagnosis of ADHD affects boys approximately three times more than girls, although boys often outnumber girls by an even greater margin in referral settings. This gender difference in referral settings is attributed to the more frequent co-occurrence of disruptive behavior disorders such as Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) and ADHD in the male population (Mercugliano, 1997). As Goldstein and Goldstein (1998) report, the externalizing disruptive behavioral problems and substance abuse that are more common in males with ADHD are stronger predictors of mental health treatment utilization than the internalizing anxiety and depression that is more likely to be seen in females with ADHD.

While there have been descriptions of the efficacy of stimulants in the treatment of behavioral problems as early as 1937, it was only after the medication treatment breakthroughs for the treatment of schizophrenia, anxiety and depression in the 1950s and 1960s that pharmacotherapy for American youth became a legitimate treatment option. Ritalin underwent clinical trails in the mid to late 1960s for the treatment of attentional and hyperactive disorders. Despite the demonstrated efficacy of this and other stimulant medications, media concerns about misdiagnosis, over-prescription, and substance abuse have precipitated efforts by state and federal agencies to limit stimulant medication of the nation's youth (Barkley, 2003).

In relation to misdiagnosis, dramatic increases in the use of stimulants over the past ten years appear, according to a broad consensus, to reflect the increased rate of diagnosis, approximating the percentage of the population identified in international epidemiologic studies as suffering from the disorder (Taylor, Sandberg, Thorley, & Giles, 1991). However, there is concrete evidence of clinical misdiagnosis. For example, Sabatino and Vance (1994) studied seventy-five 5- to 17- year olds diagnosed with ADHD and referred because of unsatisfactory treatment outcomes. The sample included those taking stimulant medications. Nearly one third were found to be misdiagnosed.

Contrary to the concern that Ritalin is over-prescribed, various researchers and studies report that only 52% to 71% of youth with a clinical diagnosis of ADHD are treated with stimulant medication "at some time before reaching adulthood" (Safer & Zito, 2000). Of those, Barkley reports between 70-80% exhibiting positive behavioral responses to stimulant medication when taken on an ongoing basis. These responses include improvements in attention, reductions in disruption and impulsivity, and an improvement in peer relations due primarily to reduced aggression (Barkley, 1990). Thus, despite widespread public concerns about the wisdom of medicating youth with stimulant medication there appears to be a consensus about its general clinical utility and appropriateness.

Parsing out whether those with ADHD are more likely to abuse substances overall, and what causal or protective role stimulant medications may play remains complex and controversial. This is not least because of the need to separate the effects of the medication from the underlying disorder or disorders mentioned above (Barkley, 1990). High levels of co-morbidity between ADHD and Conduct Disorder complicate any understanding of ADHD's role in aggressive and substance using behaviors. Conduct disorder is defined by a 'repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms are violated'. This is manifested by the presence of (1) aggression to people and animals (2) destruction of property (3) deceitfulness or theft and (4) serious violation of rules (American Psychiatric Association, 1994). Co-morbidity rates appear to be between 30-50% (Fisher, 1998). If the aggression and violence associated with CD contributes to, or is associated with elevated levels of substance use for those with ADHD (Glantz, Weinberg, Miner, and Colliver, 1999), then Ritalin's purported aggression attenuating properties may become increasingly relevant within substance use disorder (SUDs) preventative interventions. The related question of whether those prescribed stimulants are at an elevated risk for future SUDs (and consequently to possibly abuse their medications) will be explored later in the chapter.

In evaluating the scale of any potential problem with abuse or diversion it is important to note that MPH is a widely available drug. In 1996 Safer et al. reported that approximately 2.8% of children from 5 to 18 years of age were prescribed MPH in 1995. The prevalence of MPH use in this age group increased 2.5 fold between 1990 and 1995 (Safer, Zito & Fine, 1996).

Even prior to in-depth investigation, concerns about MPH abuse among adolescents seem to have some immediate plausibility. Methylphenidate is a structural analog of the amphetamines; a class of substances that have well known adverse consequences from widespread abuse and dependence (Weaver & Schnoll, 1999). Methylphenidate itself has been known as a drug of abuse among adult polysubstance users since the early 1970s. Street prices for MPH tablets consistently range around $5.00 compared to wholesale prices of around $0.28 to $1.03. Street names include 'Vitamin R' and 'Skippy'. MPH is a difficult drug to synthesize and so illegal diversion is believed to be the primary source for abuse. A DEA report from 1997 describes four different 'routes for diversion' of this drug:

1. Parents sell or abuse their children's medication
2. Adolescents sell their own or siblings meds
3. Adolescents abuse own or others meds
4. Theft from home, school, pharmacies.

Administration routes include intravenous, oral, and intranasal (insufflation or 'snorting'). It appears as though the drug is administered in different ways for different purposes ranging from performance enhancement to intense euphoria; a fuller discussion of which will be provided later in the chapter.

<u>Sensitization and Abuse Potential</u>

While there is little serious argument about the specific improvements in behavior in many treated children (Barkley, 1990), there is considerably more clinical concern about the possibility of therapeutic and non-therapeutic misuse of MPH in childhood and adolescence potentiating future substance use, abuse, and dependence. These concerns include seeking to understand the abuse potential of MPH in adolescents, and long term sensitization to stimulant drugs in the future. There are also questions about the widespread physical access to, and diversion of, a Class II controlled substance in school and home environments, because this may present (developmentally early) opportunities for substance abuse (Klein-Schwartz & McGrath, 2003). Moreover, concern has also been expressed about the vulnerability of ADHD youth to substance use disorders in general (Biederman 2003). Specifically, critics of MPH medication for ADHD youth argue that cross-sensitization with other stimulants like amphetamines and cocaine is a credible risk in a population that may already have neurological vulnerability to substance use disorders (Klein & Mannuza, 2002).

Cross sensitization is a phenomenon that occurs when previous administration of one stimulant results in greater sensitivity to the effects of another stimulant administered subsequently. This effect is postulated to be associated with neuro-adaptations that are implicated in addictive processes (Huss & Lehmkuhl, 2002). This phenomenon has been repeated experimentally with both amphetamine and cocaine (Bonate et al., 1997). It has also been demonstrated that repeated exposure to nicotine, amphetamine and caffeine, all increase later cocaine self-administration (Horger et al., 1992; Schenk et al.; 1994, and Schenk & Davidson, 1998). The implication is that early exposure to stimulants may increase drug, specifically stimulant, seeking behaviors later in life.

Yang, Swann, and Dafny (2003) found that chronic pre-exposure with MPH induced cross-sensitization effects with amphetamine in rats. However, highlighting the problems associated with generalizing animal findings to humans, these researchers found that with chronic low dose administration (analogous to human therapeutic dosing for ADHD) these rats did have locomotor sensitization, but not stereotypic behavior sensitization to amphetamine, a finding which was considered anomalous. While this can reasonably be explained by neurotransmitter effects on various neuro-anatomical sites associated with these behaviors it seems much harder to explain exactly what this finding might mean in terms of human addiction potential or human behavior in general.

Brandon at al. (2001) reported sensitization to self administration of cocaine in rats with MPH at both high and low doses. This is in contrast to Anderson and colleagues (2002) findings that preadolescent rats treated with MPH showed more aversion to cocaine than adults treated the same way. Robbins (2002) compared these studies and came to the conclusion that these seemingly contradictory results could be explained in terms of preadolescent and adolescent differences where administration at preadolescence has a protective effect that is lost afterwards (a finding that may be complementary to human studies that show a protective effect of MPH treatment at an early age on later SUD development) (Beiderman, 2003).

Despite this ambiguity, the phenomenon of sensitization has been broadly replicated in other studies. Achat-Mendes, Anderson, and Itzhak (2003) found sensitization between MPH (and to a lesser extent MDMA) and cocaine in mice. One aim of the study was to investigate the effect of MPH exposure in adolescence on cocaine induced reward and psychomotor stimulation in adulthood. Animals received intraperitoneal injections of MPH for a period approximating human adolescence. During adulthood (one month later) these animals were assessed for cocaine induced place preference (CPP); an analog for drug seeking behavior in humans. While MPH exposure initially decreased CPP during this phase, it eventually (after a two week period of extinction of CPP and cocaine use) significantly increased CPP behaviors that had been primed by the administration of cocaine. The authors suggest that this represents support for the idea that MPH use in adolescence precipitates long lasting neural adaptations, manifesting as sensitized responses to later cocaine use.

In a study where early MPH administration was used to sensitize future MPH effects, McDougall et al. (1999) found similar results with rats. Using a more compressed time frame, animals were pretreated with MPH for five consecutive days, and then assessed for intensity of stereotypic behaviors related to subsequent MPH administration. Compared to controls, the pretreated animals appeared to be sensitized to the effects of MPH demonstrating increased stereotypic behavior. This relationship was found to be dose dependent with the animals pretreated with the highest doses demonstrating the largest increases in stereotypic behaviors. Moreover, Gatley, Volkow et al. (1999) report that while cocaine equivalent doses of MPH produce higher levels of locomotor activity (at the same level of dopamine transporter receptor occupancy) both substances have very similar psychopharmacological properties.

In broad support of the idea that MPH and cocaine have similar properties, Brandon and Steiner (2003) demonstrated MPH related neural adaptation following administration to rats. They found that this regimen produced changes in gene regulation affecting expression in the striatum that are broadly analogous to the effects found by the acute and repeated administration of other psycho stimulants including cocaine.

Complementing these findings, Kuczenski and Segal (1997) sought to compare MPH with amphetamine in relation to drug induced profiles of extra-cellular dopamine, serotonin, and norepinepherine and their associated behaviors. They found (using doses of both MPH and amphetamines that produced similar behaviors in animals) that dopamine responses were broadly similar. Interestingly, they also found that MPH had no effect on serotonin levels, which seems to undermine that neurotransmitter's potential role in the induction of stimulant induced behavior.

However, moderating these findings, human research gives us a somewhat different perspective. In an earlier article that asked "Is Methylphenidate like Cocaine?" some of these same authors (Volkow et al., 1995) made the point that while the *pharmacological* action of MPH may be similar to cocaine, its *pharmacokinetics* are different, with significant implications for humans. They observed (using PET scans) that while fast MPH uptake in the human striatum consistently paralleled the experience of the reported subjective 'high', this high decreased very quickly despite significant binding to brain receptors. This contrasted with cocaine where the decline of the high was related in a more linear fashion to the fast clearance of the drug from the brain. As others have suggested (Barkley 2003), this slow clearance may have profound implications for humans in terms of the abuse potential of MPH as compared to cocaine. This should be understood in terms of frequency of administration being complementary to speed of subjective 'high' onset and drug clearance in the development of general substance abuse and dependence processes. This relationship explains why for example smoking 'crack' cocaine is more addictive than insufflated cocaine powder (Weaver & Schnoll, 1999).

In a comprehensive meta-analysis, Kollins et al. (2001) reviewed both animal and human studies looking at the use of MPH within the framework of three well established paradigms used to assess the abuse potential of drugs: self administration/ reinforcement, stimulus discrimination, and subjective effects. They found across studies that an animal will generally choose to self administer MPH over saline. However, as these authors critically outline, MPH was administered intravenously in all these subjects and the predominant route of administration for the majority of those using MPH in the general population is oral. This is a distinction that has significant pharmacological consequences ultimately producing different subjective experiences of the drug, and thus, consequently impacts the development of SUDs. Kollins (2001) also points out that while normal rat reactions to MPH may be useful in generalizing to the use of MPH in non-ADHD youth they may be fundamentally different to those in the human ADHD brain; a distinction which may be significant in differentiating MPH abuse potential for ADHD/non-ADHD adolescent humans.

So, while it may be tempting to extrapolate animal findings to humans it should probably be remembered that normal and ADHD children react differently to MPH making it difficult to generalize to the human ADHD group from the 'normal' animal group in this case. ADHD kids using MPH at therapeutic doses may simply not demonstrate the sensitization effects described above. Methodologically, this research also highlights aspects of temporal effects which may be an important dimension in understanding the development of substance use disorders. Time has shown itself to be an important factor in frequency, timing and chronicity of dosing; evolution of neuropathology and behavioral changes (Ellinwood, 1989). It is also important as we have seen, to the pharmacokinetics of a drug and in relation to developmental/neuroadaptive issues. Thus, future research should consider carefully issues such as age of first prescription, time of day (circadian/endocrinological factors), half-life of the form of MPH used, and age of first MPH abuse in the development of future drug seeking behavior.

In summary of the pharmacological literature, it is clear that there is plenty of empirical support for identifying the abuse potential of MPH, in accordance with the clinical literature, but it also clear that methodological limitations should engender caution about the broad generalization of these findings across ADHD/non-ADHD groups and across different age groups.

Does Prescribed MPH Predict future SUDs?

Having examined the experimental literature on the abuse potential of MPH, what follows is an exploration of the literature on actual outcomes for those adolescents and children who have a history of MPH prescription. This will be followed by an examination of the literature on known abuse of MPH across all sub-groups in the general population and a brief discussion of potential risk factors for MPH abuse.

An examination of the current literature seems broadly to point to MPH prescription not being predictive of future SUDs, with the added suggestion by some that it may in fact have something of a *protective* effect. Barkley (2003) did a meta-analysis of the research surrounding this topic. He describes the animal research literature on sensitization and highlights, in support of Kollins et al. (2001) critique of animal research on this topic, that the administration paradigms used are very different from the one used consistently in therapeutic use. He suggests that this distinction between oral/intravenous administration is the reason that stimulant sensitization in human ADHD children does not parallel the effects in animal studies.

Similarly, Kollins (2003) conducted a literature review of the abuse potential of MPH versus other stimulants in relation to its relevance to those with ADHD. He surmised that in studies where abuse potential was shown that using healthy or substance using subjects limits the generalizabilty of this research to ADHD youth medicated with MPH. This is particularly important in relation to the psychopharmacokinetics of MPH and its route of administration

Beiderman and colleagues (1999) found that *non*-medicated ADHD teens demonstrated elevated risk for SUDs compared to their medicated peers. It should be noted that however positive these findings may be, the time frame involved limits the ability to extrapolate to adult outcomes. This study involves a four year follow up during adolescence and thus cannot describe the effects of childhood prescription on long term adult substance use outcomes.

Faraone and Wilens (2003) did a meta-analysis of seven studies that compared stimulant treated and untreated ADHD subjects. Most of the subjects were male, severity of ADHD and comorbidity could not be equated across all studies, and definitions of substance use problems varied somewhat across studies. Despite these limitations the authors found that stimulant treatment reduced the risk of developing a SUD by 50%; reducing the risk to 'well within the normal population risk'.

More recently, Loney, Kramer, and Salisbury (2002) were able to control for the severity of disorder and comorbidity by randomization at study entry which previously presented as a major methodological problem. This longitudinal study was also able to point to a protective effect of being prescribed MPH in relation to future, including adult SUDs.

In support of these findings, Biederman (2003) suggests in his work that ADHD presents a risk in and of itself in relation to developing SUDs; that comorbidity (particularly CD) dramatically increases that risk and that MPH attenuates that risk (in subjects 15-21 years of age).

In stark contrast to the general consensus of the research described above, Lambert (Lambert & Hartsough, 1998) found that stimulant therapy predisposed youth to nicotine use in adulthood and to a lesser degree cocaine and stimulant dependence, thus, giving support to sensitization hypotheses. Barkley's (2003) criticism of this anomalous research was that methodologically stimulant treatment was essentially a proxy for ADHD (without CD being controlled for). In contrast, Millberger and associates (1997) did not find a relationship between all ADHD medication treatments aggregated together and adolescent tobacco use. Moreover, they found that ADHD teens that were still medicated were *less* likely to use tobacco than their unmedicated peers.

These contradictions prompted Barkley (Fischer & Barkley, 2003) to re-examine subjects from his own 13 year plus longitudinal study (n=147). They found that MPH treatment was not predictive of any kind of substance use (including nicotine) by mid-adolescence. However, they did find that MPH treatment did increase the likelihood of ever having tried cocaine by young adulthood, though this was mediated by lifelong CD symptoms (a significant finding due to the high rates of co-morbidity between these disorders). Overall, they found no association between MPH therapy and DSM-III-R criteria substance dependence or abuse disorders in adulthood.

Relatedly, Barkley cites Mannuzza, Klein, and Moulton (2003) who followed up on children aged 7-12 with developmental reading disorders and no other psychiatric diagnoses who were randomly assigned to MPH or placebo for 12 to 18 weeks. At sixteen year follow up, no evidence was found for supporting the sensitization hypothesis.

Thus, there appears to be little support for the idea that MPH administered to those youth with ADHD at therapeutic doses contributes to increased stimulant or other substance use. There appears to be a reasonable case to suggest that MPH in fact has a protective effect in this regard. However, one important caveat is that there is only limited evidence to suggest that this protective effect extends over the life span. One important future research question seems to be; to what extent does attenuated risk for developing SUDs in adolescence in turn attenuate risk for developing SUDs in adulthood?

Even if MPH appears to have a protective effect for those individuals who use it therapeutically to treat ADHD, it is still not without risk for that population, and the non-ADHD adolescents and (mostly young) adults who engage in the illicit use of MPH for various purposes as will be described below.

Abuse and Toxicity of MPH / Poison Center Experience

From a pharmacological perspective MPH's margin of safety is high. Side effects are often relatively easily controlled by changing the dose or times between doses. Adverse effects of overdoses are very similar to other amphetamine type drugs on both neurologic and cardiac systems. Neurologic symptoms include: irritability, agitation, euphoria, hallucinations, delusions, psychosis, and seizures. Cardiovascular symptoms include: tachycardia, hypertension, atrial and ventricular tachy-dysrhythmias, and chest pain. Hyperthermia, arrhythmias, and seizures are common in severe intoxications (Klein-Schwartz, 2002).

To what extent is MPH being abused in the general population? Poison center experience includes Foley, Mrvos, and Krenzelok's (2000) study of 113 exposures over a one year period. Of those 113 exposures, ninety one were in children nineteen or younger. In teenagers 13 to 19 years old 50% were asymptomatic. However, 73% of exposures were intentional, the majority being abuse or suicide behavior related. Indicative of substance abuse, other substances were involved in 30% of adolescent exposures.

Klein-Schwartz and McGrath (2003) tracked MPH abuse cases through The American Association of Poison Centers Toxic Exposure Surveillance System for children 10 through 19 years (n=759). Forty two percent of cases were 10 through 14 years of age. MPH only abuse cases (70%) increased sevenfold between 1993 and 1999. Symptoms were more common in cases involving other substances (84.3%) compared to those who took MPH only (71%). The most common symptoms were tachycardia (31.7%), agitation/irritability (25.7%), and hypertension (11.5%). Outcomes were measured as no effect (24.9%), mild (41.9%), moderate (32.3), and severe (0.9%). The authors concluded that health outcomes were generally good, especially for those cases involving only MPH.

MPH only exposures were more common in 10 to 14 year olds (77.2%) than in the 15 to 19 year olds (64.4%). For MPH use only the most common route was oral ingestion. Overall, they found that MPH *abuse* accounted for 11.2% of total MPH overexposure cases over this time. Significant to this study, the authors also concluded that a large majority of these abuse cases were among pre-teens and adolescents not prescribed the drug (85%).

Researchers at the University of Michigan report that in 1994 and 1995 1% of all high school seniors had used MPH without a prescription in the previous year. By 1997 that number had increased to 2.8% (reported in Sannerud & Feussner, 2000). In children ages 10-14, there appears to be a marked increase in MPH abuse since 1991, epitomized by a five fold increase in the number of emergency room visits related to MPH abuse reported nationally by the Drug Abuse Warning Network (reported in Sannerud & Feussner, 2000). By this measure, MPH appears considerably more abused than methamphetamine and slightly more abused than cocaine for this age group.

Contrasting the low toxicity implied in the poison center literature, Parran and Jasinski (1991) described intravenous MPH abuse in terms of greater systemic toxicity compared to IV cocaine and amphetamine. This was attributed to a greater quantity of water-insoluble 'incipient' constituents (Ritalin-SR 20mg was believed to be the safest in this regard by users). IV users fit a prototypical profile of older users with a long history of polysubstance use. The authors suspected that children of substance dependent parents at higher risk for ADHD were being used in prescription scams. Anecdotal reports from patients in this study suggest that these scams were widely successful across a wide range of prescribing environments, indicating a lack of sophistication by most physicians in terms of MPH's abuse potential.

Raskind and Bradford, (1973) describe a phenomenon of elevated levels of MPH abuse in a methadone maintenance program in Seattle in the early 1970s. They found MPH use to be significantly more common in this group than in a comparable group of heroin addicts using "on the street". Medical complications included superficial abscesses and cutaneous ulcers at injection sites, bacterial endocarditis, pulmonary granulomatosis secondary to inactive ingredients in the tablets, and toxic paranoid psychotic reactions. Initiation of this use was often associated with attempts to counter drowsiness associated with initial methadone use. However, use persisted beyond this time which was attributed to the euphoric properties of injected MPH. With physiological dependence under control these addicts were still seeking a euphoric "rush" which MPH could provide without the risks of depressed respiration that came with injected sedatives. This tended to perpetuate needle use which presented ongoing health risks. Clinicians also noted that MPH habits of $100 per week (at about $4 per tablet) were not rare and that this financial burden tended to contribute to further criminal activity. MPH also had the 'advantage' of not being screened by most urine analysis tests used at that time. This paper also referred to a study at the University of Oregon at Portland that estimated that 20% of the methadone program participants were also injecting MPH at that time (1972).

Another study from the early 1980's (Haglund & Howerton, 1982) examined MPH abuse in a clinical population suggests that this drug was continuing to be used by a polydrug and methadone using population particularly in West Coast cities and that it was associated with health problems and poorer outcomes for methadone maintenance users overall.

Despite the perception that combining MPH and alcohol seems relatively safe, (Klein-Schwartz, 2002) there appears to be the possibility of toxic interactions leading to increased morbidity and mortality (as with combining cocaine and alcohol). Markowitz, Logan, Diamond, and Patrick, (1999) reported the discovery of the novel drug metabolite ethylphenidate in two overdose fatalities involving MPH and alcohol consumption. Further studies of the role of this metabolite were recommended.

A review of the literature only resulted in one other case example of a fatality due to the intranasal abuse of MPH. Masselo and Carpenter (1999) report that a 19 year old male had been 'snorting' MPH and drinking beer at a party when he suddenly lost consciousness. By the time he arrived at the hospital he was in full cardiopulmonary arrest, and was deemed to have experienced severe hypoxic brain damage. After sixteen hours he was noted to be asystolic and was declared dead. Postmortem revealed that though blood tests at hospital admission revealed MPH concentrations roughly within the therapeutic range, metabolites suggested levels about 2 to 3 times conventional therapeutic levels. Alcohol was the only other drug detected. It was determined that he did not take MPH as part of a therapeutic regimen, and that he did not abuse the drug on a regular basis. There was no indication in this report of any known pre-existing cardiac vulnerability. While other fatalities have been reported with intravenous use involving much higher levels of MPH in the blood, this report suggests that fatal consequences are possible for a very different kind of abuse pattern that is reportedly becoming increasingly common. This pattern is described by MPH being snorted or eaten while drinking alcohol recreationally by adolescents and young adults who may not typically meet criteria for abuse and dependence and who may believe that the drug they are using is relatively risk free.

The particulars of MPH abuse patterns are scarce in the literature. Garland (1998) gave a rare detailed case example of intranasal abuse of prescribed MPH. This 15 year old patient appeared in crisis after a 2 week binge of Ritalin abuse. Each dose comprised of three crushed 20mg Ritalin-SR tablets to produce a euphoric state. This was repeated two or three times in a 24 hour period, followed by 14 to 16 hours of sleep before repeating the pattern again. Symptoms of intoxication included feelings of paranoia and hypersensitivity to sensory stimuli as well as the desired euphoric effect. The youth and his friends who had all experimented previously with alcohol, marijuana, and hallucinogens had been pocketing their medications and saving them for recreational use. When his parents discovered his missing medication, he behaved very atypically; showing both tremendous fear of the police and suicidal ideation. His subsequent behavior included hypersomnia, depressed affect, and ravenous hunger. The author described this pattern as consistent with amphetamine withdrawal. While there appeared to be few medical complications with this case, the post-intoxication depressive state and suicidal ideation in an impulsive youth should be concerning.

This last example, one of the few in the literature, highlights several things. First, that MPH abuse can go undetected for some time. Second, that despite the fact that abuse of medication among those prescribed it appears to be relatively uncommon, the increased risk of using substances that ADHD youth as a whole appear to be at (whether secondary to highly comorbid disorders or not) needs to be a concern to those supervising medications as they appear to be easily available for abuse. Recommendations include not only taking inventory for missing medications but that medications are also taken as prescribed in a supervised way and not horded for later use.

Recreational Use of MPH in a College Student Population.

There are a small number of studies that describe post-adolescent college student MPH abuse. In the earliest systematic study of MPH abuse in this population, Babcock and Byrne (2000) administered a survey of recreational MPH use at a New England public liberal arts college. They found that more than 16% of the sample (n=283, a 20% return rate) had used MPH recreationally. Of note, 12.7% of the total sample (nearly 80% of those who had used MPH recreationally) had administered the drug intranasally. This pattern was more common among traditional age students (20.9%) than those over 24 (3% of the sample) and was approximate to levels of cocaine and amphetamine use for that younger age group. In fact, no student over 25 had used the drug without a prescription. These non-traditional students were not drug naïve, and in fact were more likely to have used amphetamines or cocaine recreationally. Interestingly, while over 65% of the sample under 24 yrs knew at least one student who had used MPH without a prescription, only 36% believed that MPH was a 'drug of abuse' on campus. This belief was held despite the fact that over 58% of the sample knew at least one student who had 'snorted' MPH. This seems to indicate a widespread belief in the relatively benign nature of this drug. The researchers suggest that a significant proportion of the students used MPH to improve academic performance, based upon personal communications. Unfortunately this study did not provide any data on frequency or severity of use. Only 1.8% of this sample had a prescription for MPH.

The next study (Graff-Low & Gendaszek, 2002) was conducted at a small competitive liberal arts college in Maine. Subjects were from undergraduate psychology classes. Of 160 surveys administered 150 were returned. The gender distribution for returned surveys was equal. In this study 35.5% of students reported using "prescription amphetamines" without a prescription. Even taking into account the slightly different criteria used between this and the study above (Babcock & Byrne, 2000) these results are striking. 19.3% reported using prescription stimulants with alcohol for recreational purposes. 34% of the sample had used MDMA or cocaine in the last year. These authors suggest that pressures to perform at a competitive liberal arts college encourage the use of drugs that may improve cognitive performance in the short term.

In an investigation of anecdotal reports of college students taking MPH to increase their party stamina and to facilitate drinking Barrett and Phil (2002) contacted 17 MPH abusers through a community snowball sampling method. Sixteen of these chronic users reported that the primary route of administration was oral; the seventeenth ingested it intranasally (in contrast to Babcock and Byrne's (2000) findings above). The drug was typically consumed in several small doses over the course of a drinking session. They also reported that only two of the seventeen subjects reported that they had a prescription for MPH. Positive effects of mixing these substances were described as 'increased euphoria and energy as well as a diminished sense of drunkenness'. Six of the subjects likened the effect to combining cocaine and alcohol.

The most substantial study on patterns of misuse in a college population was done by Teter et al. (2003). A random sample of 3500 students from a student body of approximately 21,000 was chosen at the University of Michigan. Of those 3500, 2250 completed the web-based survey (a 64% return rate). Of these, only 3% reported past year illicit MPH use. This is a finding consistent with findings from the Monitoring the Future study of 12th graders. Of the 57 students who had reported illicit MPH use, 2% began taking MPH in junior high, 19% in high school and 79% in college. Unfortunately, no information on route of administration was collected. This pattern of misuse was distributed equally across gender, and was also significantly associated with other recreational drug use (including nicotine). Again, this study did not assess motivation for use, frequency and intensity of use, or rates of insufflation vs. oral administration.

Overall, these studies point to marked differences in both the rates of misuse and routes of administration for college students. No literature could be found which could explain these significant differences. This could be due to very local cultures and norms of drug abuse, or it could be due to regional differences, or other environmental demands. That these discrepancies can exist unchallenged in this very limited literature points to the very preliminary nature of research on MPH abuse and the need for further large scale studies.

Having attempted to describe the characteristics of abuse for different sub-groups, and the factors that may affect the abuse potential of MPH, the following section will seek to describe factors that may theoretically be predictive of MPH abuse.

The Role of Nicotine

While no literature could be found on the role of the use of nicotine in the abuse of MPH in ADHD and non-ADHD youth, it will be important to clearly identify the possible role of nicotine use as a predictor of MPH abuse for preventative purposes if it does exist. It may also be that nicotine users with concomitant ADHD are differentially at risk for developing SUDs and MPH abuse in particular. This will also be important to identify.

While there are extremely limited reports on the relationship between nicotine and MPH there does exist a literature on the ADHD/nicotine relationship that may have relevance to this study. Sullivan and Rudnick-Levin (2001) found that nicotine dependence among adults with ADHD was substantially more common (40%) than in the general population (26%). Another smoking study found that adolescent ADHD inattention symptoms increased the likelihood of current smoking 180% even after controlling for peer smoking behavior (Tercyak, Lerman, & Audrain, 2002). Yet another study supports the idea that inattentive symptoms are predictive of smoking behavior after controlling for CD and other factors related to adolescent smoking (Burke, Loeber, & Lahey, 2001). These researchers found that inattention increased risk of smoking by 130% in early adolescence. Overall, they found a full 51% of their ADHD participants reporting tobacco use.

Milberger, Biederman, Faraone, Chen, and Jones (1997) found that use of nicotine increased the risk of developing a SUD five times for those teenagers with ADHD. Others (Disney et al. 1999) have found main effects for ADHD and nicotine for predicting substance use after controlling for CD. However, Gittelman, Mannuzza, Shenker, and Bonagura (1985) found that elevated levels of nicotine use for ADHD youth were mediated by the presence of conduct disorder.

It has been noted that nicotine dependence in those with ADHD has been particularly hard to treat. This has been attributed to nicotine's ability to reduce the symptoms of ADHD (Coger, Moe, & Serafetinides, 1996). Of particular relevance to the present study is the suggestion that there exists a synergistic interaction between nicotine and MPH in increasing extracellular dopamine, which in turn may go some way towards further explaining elevated levels of smoking for this group (Gerasimov et al., 2000) and theoretically may present an elevated risk for prescribed MPH abuse. However, a recent longitudinal study (Whalen et al., 2003) found that MPH prescription predicted *lower* nicotine use compared to an equivalent non-medicated ADHD group. The authors feel that their findings substantiate the *self medication hypothesis* in the unmedicated group, while contradicting the *gateway hypothesis,* in that their findings did not suggest that MPH prescription increased the use of nicotine. More generally, it will be interesting to see if nicotine use within the MPH prescribed group, will also manifest as a significant predictor for MPH abuse.

Aggression and MPH Abuse

The question 'does aggression predict MPH abuse?' is an empirical one as there was no literature found which could address this question. However, as this a question that will be assessed in a correlational rather than a causal fashion in this study, it will be important to address a possible conceptual misunderstanding of potential results beforehand.

Firstly, while this study will concern itself with aggression as a predictor of a specific kind of substance use, it is important to highlight that the relationship between broad categories of substance use and aggression generally is complex (Maletzky, 1976) and any correlation between them should (at the least) be considered bi-directionally in terms of any potential causal relationships. For example, while the relationship between alcohol, violence, and victimization has been the most strongly documented, it has been suggested that this is secondary to disinhibition and impaired social judgment (Volavka & Citrome, 1998; Conacher 1997). This is reinforced somewhat by physiological research that does not support the idea that smaller amounts of alcohol in and of themselves would produce EEG changes that would correlate with aggressive behavior (Maletzky 1976).

Animal research seems to confirm and expand upon this complexity. Specifically, *stimulant* effects appear to be variable depending on the species, the individual's experience with aggression, the dose of the drug, and the animal's social position in a group (Volavka, 1995). While psycho-stimulants, phencyclidine (PCP), cannabis, opioids, benzodiazepines, and anabolic steroids have all been associated with increased aggression under varying circumstances (for review, see Volavka and Citrome, 1998) no direct neurological mechanisms on aggression are observed. There appear to be no substances of abuse that specifically promote (or inhibit) violent behavior through their pharmacological effects alone. The direction and size of effects on aggression appear to depend on factors including the dose, personality of the user, expectations, and experience with the substance, brain disorder, or social context (Volavka & Citrome, 1998). Still methodological concerns remain; it appears as though no research to date accounts for neurological mechanisms of poly-substance use which due to this being a very common phenomenon (including MPH with alcohol) presents a serious limitation on the study of this subject. Despite these equivocal findings on the relationship between aggression and drug use, it will be important to assess their importance as a core measure of anti-social behavior. While it may not be conceptually clear what the role of aggression may be in terms of causation in a study like this, it will be important to be able to control for its effects within statistical analyses.

Summary

To summarize, MPH is a stimulant medication effective in the treatment of several clinical disorders, particularly ADHD. Its widespread use amongst adolescents has attracted both controversy and concern. Despite these concerns, it appears as though MPH is a largely safe and efficacious medication when used therapeutically. It does not appear to be systematically over prescribed, nor does ADHD appear to be generally misdiagnosed on a large scale.

While animal research appears to largely substantiate the abusability of MPH and the risk of further 'sensitization' to other abused psychostimulants, caution needs to be exercised in generalizing these findings to humans, particularly those receiving therapeutic doses for ADHD. Criticism of animal model research focuses on administration paradigms, neurodevelopmental issues, and generalizability issues due to the therapeutic MPH reaction in the human ADHD brain. However, while the vast majority of therapeutic users may even be seen to enjoy protective effects of MPH in guarding against adolescent SUDs, long term effects need to be further delineated through further longitudinal study.

Also, while ADHD itself is arguably a risk factor for developing SUDs, highly co-morbid conditions of ADHD such as conduct disorder appear to combine to produce an even more elevated lifetime risk for developing substance use disorders thus at least theoretically putting those individuals at risk for abusing their medication.

It is also true that MPH has a long history of being abused. Outcomes of this abuse seem to largely be a function of route of administration and other substances used. While generally pharmacologically safe, MPH presents particular risks for intravenous users, and has potentially elevated risks for those abusing it with alcohol. While not yet substantiated, there is a suggestion of cardio-toxicity with this combination similar to that of cocaine and alcohol where even moderate use may have potentially fatal consequences for those with (possibly unknown) cardiac vulnerability. This is particularly relevant because of the apparent perception of MPH's harmlessness among many of the young people who use it. These people may be in the very early stages of drug experimentation, or they may be older; with or without significant SUD symptomology. In any case, widespread availability of MPH and the perception of relative harmlessness may contribute to further widespread abuse with possibly tragic consequences.

MPH abuse does appear to be on the rise overall but findings from the various studies on this are not necessarily consistent with each other. It appears as though there are presently several classes of users and routes of administration. While the taxonomy of MPH abuse is in a very preliminary state there are several distinctive categories suggested by the literature that can be tentatively outlined. There appear to be some school age youths abusing their medications, and a larger group of youths who are using it without prescription. These two groups seem to be largely insufflating MPH for its euphoric (cocaine or amphetamine-like) effects. Tentatively, there also appears to be fairly widespread MPH abuse within a college population. These users are either seeking to improve academic performance using MPH by (mostly) oral administration, or who are seeking euphoric effects and/or to improve their 'partying' stamina, whereby administration is either oral or intranasal and usually involves the co-administration of alcohol. This pattern of use is described by users as being similar to that of cocaine and alcohol. There does not necessarily have to be correlated indications of drug related problems in this group and the perception of the relative harmlessness of MPH appears to be commonplace. There also appears to be a more polysubstance using older generation of people who are abusing MPH and are at a higher risk for meeting criteria for substance use disorders. They may be (successfully) 'scamming' the system using their own children, or buying redirected MPH 'on the street'. Whether there is any significant pattern of progression between these types of use across the life span can only be outlined by future longitudinal research.

Lastly, aggression will be assessed in this study in an exploratory and correlational fashion as no literature exists on its role in the abuse of MPH, and it provides a rudimentary proxy for the presence of conduct disorder. While it appears as though ADHD is a risk factor for nicotine use and consequent SUDs, it has also been shown that MPH reduces nicotine use in ADHD subjects to some significant extent. Nicotine's role in MPH abuse is open to empirical question with the suggestion that nicotine and MPH may be acting synergistically in attenuating attentional problems in those who have been prescribed MPH for ADHD. Whether nicotine use is a significant predictor of MPH abuse will be addressed in the current study.

The Present Study

This study is intended to provide both large scale epidemiological information on the extent of MPH abuse in school age children from grades 9 through 12 and to provide some evidence of significant correlates that may help to define the characteristics of MPH abusers and aid the development of preventative strategies.

Firstly, it will be important to identify the extent of MPH abuse in an age group that comprises a significant proportion of exposure cases seen in Poison

Control Centers nationwide (Klein-Schwartz & McGrath, 2003). The present study will serve to elucidate national trends. It will not however, be able to describe regional trends. For example, it is not clear at this point if the variability in the college data on MPH abuse is related to type of institution or geographical differences or whether these differences if they do exist generalize in any meaningful way to the school age children in this study.

It will also be possible to begin to identify the role of the use of other substances in the abuse of MPH. This question can be understood in terms of whether young MPH abusers are relatively drug naïve or not.

It will be possible to break this sample down developmentally into two broad age (grade) groups. This will help to elucidate the age-related trajectory of MPH abusers.

More specifically, it will be possible to compare age, gender, style of drug use, types of aggression, and nicotine use, to identify particular risk profiles for these youth.

While gender differentials are a known quantity in terms of the diagnosis and treatment of ADHD, it will be possible to identify gender as a risk factor for MPH abuse.

It is expected that intensity of use of other substances will be a significant predictor of MPH abuse.

It is also expected that nicotine use will be a significant predictor of MPH abuse. It is also tentatively expected that this predictive power will be more powerful for MPH prescribed youth versus non MPH prescribed youth.

Moreover, it is further expected that physically aggressive behavior will be predictive of MPH abuse.

CHAPTER II

METHOD

Participants

Participants were 17,000 male and female high school students in grades 9-12. The participants were from schools across the country that elected to administer the American Drug and Alcohol Survey (ADAS) through a private firm in Colorado (Rocky Mountain Behavioral Sciences Institute Inc.) in the 1999-2000 school year. While this is a sample of convenience as opposed to a purposive sample, it has an extremely large number of participants with a wide geographic distribution. Previous investigation (Oetting & Beauvais, 1990) has shown that the drug use prevalence rates from the ADAS closely match those obtained from the Monitoring the Future (MTF) survey from the University of Michigan (Bachman, Johnston, & O'Malley, 2001). The MTF uses a two-stage probability sample of youth enrolled in schools across the U.S. The demonstrated similarity between the results obtained from the ADAS and the MTF makes a compelling case for the use of the ADAS to study drug use and associated behaviors within a representative population of high school youth. Many of the items of interest for this study are available only in the ADAS database.

There is a memorandum of agreement between the Tri-Ethnic Center

(TEC) at Colorado State University and RMBSI, which allows the TEC access to its database for research purposes. The surveys were administered during a regular classroom period by the classroom teachers. The surveys are anonymous and precautions were taken to insure that students could not be linked with their answers. Students were instructed that their participation was completely voluntary and they could refuse to answer any, or all, of the questions without penalty. Aggregate rates of refusal to take the survey were generally under 4%. When the surveys were completed they were placed randomly in an envelope or box which was immediately sealed and returned to RMBSI. Each school received a comprehensive report on the results obtained for their students.

Instruments

The ADAS is composed of items measuring drug use and the broad dimensions of psychological, social, and cultural functioning for adolescents in school. The survey has been developed and refined over the last 25 years and has demonstrated good psychometric soundness. All questions were asked in English as reading abilities in other languages were assessed to be commensurate with English reading abilities. The items that were used in the present study were extracted from the larger pool of items on the ADAS.

Demographic items The demographic variables age, gender, and racial identity consisted of individual ADAS items.

Ritalin Abuse This is the dependent variable for this study and consisted of an item asking if the participants had used Ritalin to get high in the last 12 months. The response options were; No; 1-2 times; 3-9 times; 10-19 times; 20-49 times; 50 or more times.

Ritalin Use This variable consisted of an item asking if the participants had ever been prescribed Ritalin. The response option was a dichotomous "Yes", "No".

Smoking Behavior This data is obtained by asking if the participants smoke cigarettes. The response options were; not at all; once in a while; 1-5 times a day; half a pack a day; a pack a day or more.

Substance Abuse This is a composite scale derived from the ADAS items that query the participants about their overall involvement with drugs (Oetting, Beauvais, & Edwards, 1985). The scale measures quantity, frequency, and patterns of use for an assortment of substances including alcohol, marijuana, hallucinogens, cocaine, heroin, and barbiturates. There are 10 items measuring alcohol use, and an additional 11 items for other drugs. The substance involvement scale is comprised of items that assess use of the substance in the last month, how the substance is used (e.g., how do you like to drink alcohol? ...I never do it, just a glass or two, enough to feel it a lot, until I get really drunk) and self-identification as a user (e.g., In drinking are you… a non-drinker, a very light drinker, a moderate drinker, a heavy drinker, a very heavy drinker?). The scale has been tested on minority and non-minority youth and reliabilities are very consistent across samples (Oetting & Beauvais, 1990). The components of the scale (i.e. level of involvement with individual drugs) had overall Cronbach Alpha reliabilities ranging from .80 to 90. These ranged from .74 to .92 for Mexican American Youth and from .78 to .96 for Anglo American youth (Oetting & Beauvais, 1990).

Validity is demonstrated by a clear linear relationship between the level of drug involvement and levels of major risk factors associated with drug use. These factors include family problems, school achievement, peer deviance, and psychosocial measures. Validity is also demonstrated by low rates of reporting use of a fake drug

(<2%) and exaggerated (<5%) or inconsistent response patterns (4%). Several other measures such as scale inter-correlations, age group norming and, scale discrimination, also demonstrate validity and reliability for the drug grouping scale as well as the substance-specific scales (Oetting & Beauvais, 1990; Oetting, Edwards, & Beauvais, 1985).

Aggression Aggression was measured by the following four scales, which together comprise the 12 item Anger Expression Scale (Deffenbacher & Swaim, 1999). These scales are embedded as potential responses to a single item stem on the ADAS. This includes the Verbal Assault (VA) scale comprising four verbally abusive items (i.e., telling people off, cursing, saying nasty things, and being sarcastic), the Physical Assault – Objects (PAO) scale comprising four items with expression directed towards things and the physical environment (i.e., slamming doors, throwing things, banging things, and stomping around), and the Physical Assault –People (PAP) scale comprising four physical items (PAP) with other people as the target of expression (i.e., hitting others, shoving others, trying to hurt other people physically, and getting into fist fights). These items were chosen in response to the stem, "when I get angry, I...". Items were intermixed and responded to on a 4-point Likert scale (1 = never, 2 = not much, 3 = some, and 4 = a lot). In developmental studies by Deffenbacher and Swaim, initial Cronbach Alpha reliabilities for the VA scale were between .82 and .84, for the PAO scale between .82 and .86, and for the PAP scale between .88 and .91. For the current study, they have been calculated at .83 (VA), .92 (PAP), and .85 (PAO) respectively, with a full scale reliability of .92. Factor correlations between these subscales originally ranged between .55 and .87. Although these correlations were generally high, sufficient independence between these constructs was demonstrated to justify using these categories to make distinctions between different kinds of aggressive behaviors, particularly across dimensions of age, gender, and ethnicity (Deffenbacher & Swaim, 1999).

Statistical Analyses

Because of the nature of the data and the hypothesized relationships between the variables, multiple regression has been chosen as the most appropriate analysis for the purposes of this study. However, due to the hypothesized significant relationship between MPH prescription and nicotine use and the possibility of a significant interaction effect of these on the dependent variable of MPH abuse, an interaction term will be added to the regression equation. If the joint term for this interaction is found to be significant, post-hoc testing will be conducted to assist in its interpretation. This post-hoc testing will be conducted by testing simple slopes for nicotine use within MPH prescribed and MPH non-prescribed groups. While analyzing the interaction of continuous and categorical variables has traditionally been the province of ANOVA type analyses, the method of using a 'median split' has been shown to 'throw away' information thus reducing the power of the analyses to detect interaction effects. Consequently, this study will use the 'dummy coding' methodology proposed by Aiken and West (1991) to adequately test and interpret categorical/continuous interactions within multiple regressions.

Initially, frequencies and means for the subject demographics and other variables of interest will be provided. Following this will be the provision of reliability analyses (Cronbach Alphas) for all the scales used. It is believed that it is prudent to do this to compare these obtained values with previous estimates of reliability. This will be followed by the provision of correlations between all the variables prior to doing the multiple regressions themselves.

In addition to the multiple regression with interaction term, a discriminant analysis will be run determine classification of membership into three groups: those with a history of MPH prescription who are abusing MPH; those with a history of MPH prescription who are not abusing MPH; and those without a history of MPH prescription who are abusing MPH. This will serve to complement the information obtained from the multiple regression and to provide information relevant to preventative strategies for those groups.

All of the data for this analysis has been checked for inconsistent and exaggerated responses.

CHAPTER III

RESULTS

The final sample comprised of 17,000 students from grades nine through twelve. Males and females comprised 47.7 and 50.0 % (2.3% of the sample missing gender data) respectively of the total sample used. However, males and females comprised 67.6% and 29% respectively of those who responded as having a history of MPH prescription. This finding is congruent with epidemiological findings of the ratio of males to females with ADHD (Barkley, 1991). The frequency for youths who had abused MPH was 6.4% for the total sample (n=17,000).

Another preliminary analysis (independent sample t test) considered differences between groups divided by grade. One group comprised grades 9 and 10, while the other comprised grades 11 and 12. Group differences were not significant for the dependent variable of MPH abuse (p=.06). A second preliminary analysis eliminated history of MPH prescription as a useful variable in the final regression.

Prior to running the multiple regression, Pearson correlations were computed between all the variables. Within a multiple regression, beta weights indicate the amount of variance explained by a variable while controlling for all other variables entered at that point. However, it is important to understand the degree of relationship between variables as a background for this. To this end, correlations between all variables can be seen in Table 1. This table serves to illuminate how the predictive power of variables changes as further variables are entered stepwise into the model due to varying levels of shared variance. Noteworthy are the Pearson correlations between style of drug use and smoking cigarettes ($r=.56$, $p<.001$), and abusing MPH and the interaction of MPH prescription history and smoking ($r=.34$, $p<.001$).

Next, a forward stepwise multiple regression (with interaction) was run using MPH abuse as the dependent variable. While this kind of model building is sometimes controversial because of its atheoretical and data driven method of entering variables, it is appropriate for a large exploratory study of this kind (Cohen & Cohen, 1983). The number of variables for this analysis was carefully limited, being driven by consideration of the relevant literature. Consequently it was expected that most if not all of the posited predictors would remain in the final model. This proved to be the case, with only two variables (gender and physical assault on an object) failing to be included in the fifth and final stage of the analysis. Exclusion of variables was based upon the F statistic (probability of F to enter $<=.05$, F to remove $>=100$). While concerns have been raised about the potentially misleading nature of these significance tests (Wampold & Freund, 1987), they were deemed appropriate in this case because of the small number of variables not retained in the final model. Thus, at the end of this analysis, five variables were significant in their predictive power; style of drug use ($p<.001$), the (smoking/MPH prescription history) interaction term ($p<.001$), smoking ($p<.001$), physical assault on a person ($p<.001$), and verbal assault ($p<.05$). Gender and physical assault on an object did not come close to significance. This final model's beta weights, standard error, and significance levels can be seen in Table 3.

While five of the original seven variables were found to be significant predictors of MPH abuse in this sample, this should be nuanced by an examination of the amount of variance explained by the addition of each additional variable into the model. The amount of variance in MPH prescription predicted by the addition of each variable can be seen in Table 4. By observing this statistic across the five steps of the regression it can be seen how much R square change there is for the model with the inclusion of each additional variable. Thus, style of drug use accounts for 81.4% of the explainable variance in MPH abuse, the interaction between a history of MPH prescription and smoking adds on approximately another 17.1%, smoking adds another 1.6%. Physical assault on a person contributes about) 0.8% and verbal assault contributes nothing more. While verbal assault (VA) is statistically significant at the .05 level, the others variables are significant at the .001 level. Therefore, it does not, in reality, contribute much more variance in terms of predicting a history of MPH prescription; its inclusion in the model is attributed to statistical power due to the size of the sample. This variance explained stepwise in the regression model can be seen in Table 4.

Due to the hypothesized significant relationship between MPH prescription and nicotine use and the possibility of a significant interaction effect of these on the dependent variable of MPH abuse, an interaction term was added to the regression equation as part of the step-wise regression. The joint term for this interaction was found to be significant ($p<.001$), and post-hoc testing was conducted to assist in its interpretation. This post-hoc testing was conducted by testing simple slopes for nicotine use within MPH prescribed and MPH non-prescribed groups. While analyzing the interaction of continuous and categorical variables has traditionally been the province of ANOVA type analyses, the method of using a 'median split' has been shown to 'throw away' information thus reducing the power of the analyses to detect interaction effects. Consequently, this study used the 'dummy coding' methodology proposed by Aiken and West (1991) to adequately test and interpret categorical/continuous interactions within multiple regressions. This analysis found that having been prescribed MPH was far more predictive of smoking (R square=.186) than not having been prescribed MPH (R square=.06) (see Table 2).

In addition to the multiple regression, a discriminant analysis was run to determine how well the variables discriminated between three groups: those with a history of MPH prescription who are abusing MPH; those with a history of MPH prescription who are not abusing MPH; and those *without* a history of MPH prescription who are abusing MPH. Discriminant analysis successively identifies the linear combination of attributes, known as Canonical discriminant *functions*, which contribute maximally (each function is orthogonal) to group separation (Grimm & Yarnold, 1995). Before discriminant functions were generated, differences between the three groups were tested using the Wilks' lambda statistic, resulting in a statistically significant ($\Lambda = .64, p < .001$) ability to discriminate between the three groups (see table 8). Then, to establish how many derived functions were useful, the following information was considered: eigenvalue, relative percentage of the predictable group variation, canonical correlation coefficients, and chi-square tests. The pair of discriminant functions derived in this analysis were both found to be statistically significant ($\chi^2=566.3, p<.001$), accounting for 100% of the predictable between groups variation using these variables (Table 5). Thus, for this study, both functions are useful, enabling discrimination between all three groups using the variables involved. Group means (or *centroids*) identified which functions discriminate between which groups (statsoft.com). Function 1 discriminates between the two MPH abusing groups (MPH prescribed and non MPH prescribed) and the MPH prescribed non-abusing group. Function 2 discriminates between the two MPH using groups (Table 5).

While the second function was statistically significant (p<.001), it explained 3.9% of the variance predicting discrimination between groups, compared to the 96.1% of the variance explained by the first function (Table 5). Also, the eigenvalue (the ratio of the between-groups sum of squares to the within-groups sum of squares) is 24.8 times larger for the first function compared to the second. These ratios describe the degree of difference in the variable's ability to discriminate between the two MPH abusing groups (MPH prescribed and non MPH prescribed) and the MPH prescribed non-abusing group.

Two types of coefficients were used within each function in interpreting this descriptive discriminant analysis; *structure* coefficients, and *standardized function* coefficients. *Structure* coefficients are the within group bivariate correlations of each variable with the canonical function, while the standardized *function* coefficients reveal the relationship between the entire model and the individual variables. Both scores are considered central to DDA analysis (Huberty1994). However, while the standardized function coefficients describe the unique (partial) contribution of each variable to the discriminant function(s), the structure coefficients describe the simple correlations between the variables and the function(s). Thus, in describing meaningful labels to the functions structure coefficients should be used. When seeking to describe the contribution of each variable to the function, standardized function coefficients should be used (Statsoft, 2004).

So, Function 1 is best described by the 'style of use' variable (absolute correlation of .94) and cigarette smoking (absolute correlation of .62.) (Table 7).

Therefore, the ability to differentiate between those who abuse MPH (prescribed and non-prescribed) and those who have been prescribed MPH but do not abuse it is best defined by an individual's drug taking and smoking behavior. The ability to differentiate between the MPH abusing groups is best defined by physical aggression against a person (absolute correlation of .79) and gender (absolute correlation of -.70) (Table 7). An examination of group means (Table 9) shows that it is the group with an MPH prescription history that is associated with high scores on these variables.

In consideration of the variables that explain the large majority of the variance in this case, *standardized function* coefficients revealed that style of use (.86) and smoking (.26) made the largest contribution to discriminating between the three groups on the first function, followed by physical aggression (-.04) and gender (.24). On the second function, physical aggression against people (PAP) had the largest standardized function coefficient (.72), followed by being male (-.61), then cigarette smoking (-.09) and finally style of drug use (.02). Function and structure coefficients for both discriminant functions can be seen in Tables 6 and 7, respectively.

It should be noted that violations of homogeneity of matrices and univariate normality were observed but were not considered threatening enough to abandon the analysis. For example, a Bartlett's Box-M test of equality of covariance matrices produced log determinants (products of within group covariance matrices) that looked unremarkable but which produced a significant Box-M (p<.001). This unequal covariance statistic can be attributed to multivariate normality being violated, or within group sample sizes being large in relation to the number of variables (Grimm & Yarnold, 1995).

It has also been suggested by others using the Box-M statistic that these violations can meaningfully be as much attributed to the sensitivity of the test as to statistically significant differences among groups. This suggestion is founded to an extent on the belief that the sample is representative of the population and that the linear composite is usually normally distributed even when the dependent variable groups taken individually are not (Ittenbach et al., 1993). In the present study, it appears from an examination of the log determinants that it is the 'prescribed/didn't abuse' group that accounts for the difference. A more detailed picture of these differences can be seen by examining the means and standard deviations all the variables across groups (Table 9).

CHAPTER IV

DISCUSSION

In establishing a baseline for understanding this study's results it is important to first compare the present study's findings with other estimated rates of MPH prescription. In this 1999-2000 school year sample, *lifetime* prevalence for history of MPH prescription was about 7.4%. This can be compared to a range of findings that describe 1.3% to 7.3% of school age youth taking stimulants for behavior management (Barkley, 2003). On the high end of this spectrum Safer, Zito, and Gardner (2004) found differences within a Mid-Atlantic state (private 4.3%, Medicaid 7.3%) between types of insurance with co-payment requirements being posited as an explanatory factor. Moreover, Musser et al. (1998) describe wide variation in prescribing practices in Michigan, where the use of MPH has exceeded the national average by approximately 80% from 1981 through 1992. They found that half the prescriptions for MPH were written by 5% of the pediatricians in the state. All of this variation makes aggregate measures difficult to interpret.

It is also worth further exploring some of the demographic data obtained in the current study even if they did not affect the outcome of the study. While large sample population based epidemiologic studies in this area are few in number, those we do have seem to indicate that not only are ADHD prevalence and MPH prescription rates probably significantly higher than previously believed, they also differ by both SES and ethnicity. In one 1998 study, stimulant prescription prevalence estimates ranged widely, from 18.3% for high school white males to 3.4% for African American females (Rushton & Whitmire, 2001). Roughly consistent with the much lower 2.7% prescription history rate for African-Americans in the current study (see Table 2), Zito et al. (1997) showed in a Maryland Medicaid study that African-American youths had a rate of MPH prescription 2.5 times lower than white youth. Similar findings were found in several Virginia school districts (LeFever et al., 1997). This basic trend was also supported by a nine-year longitudinal study of 177 clinic-referred boys (Burke, Loeber, & Lahey, 2001).

So, comparing both MPH prescription rate ranges and demographic breakdowns from other studies, the significant proportion of youth with a history of MPH prescription in this sample can thus be broadly compared to the point prevalence values found in other studies cited above. Clearly the different estimation methods can account for some of the differences shown, but the lack of a point prevalence estimate still represents a limitation of this study. It cannot be known at this point how many students in this study are currently receiving MPH medication.

Also it should be noted that within the geographically aggregated figures in this study there probably lies significant regional variation. Cox et al. (2003) found in a well controlled study using a commercially insured (non-Medicaid) sample, that children living in the Midwest and South were 1.55 and 1.77 times more likely to consume at least one stimulant medication than children in the West. The significance of this for this study lies in further understanding variables that may account for these elevated rates of prescription because they may also account for MPH abuse. This needs to be the topic for further study.

Despite concerns about lifetime versus point prevalence, and supporting the use of lifetime prevalence data for MPH prescription; this study does give a clearer sense of the total amount of youths who have been exposed to MPH at some time in their lives. This may be a more relevant issue when it comes to concern about sensitization for future or further stimulant abuse. This issue could be nuanced in further studies by examining age of first prescription as a factor, while controlling for other behavioral variables that might potentially account for some of the variance in explaining future MPH abuse (e.g. aggression and oppositionally defiant or conduct disordered behavior).

In relation to gender and prescription rates, this study found a 2.3:1 ratio between males and females who have been prescribed MPH. This is in contrast to Cox et al.'s (2003) findings that would suggest that the ratio should probably be closer to three to one. This finding may represent the narrowing of the male to female gap in stimulant prescription attributed by Cox et al. to greater levels of diagnosis of the predominantly inattentive type ADHD that is more common in girls. However, the findings within this study are *lifetime* prevalence estimates for *older* children, making this claim somewhat harder to support. Still, as an aggregate measure, possible relevance for the use of lifetime prevalence rates in the current study lies in implications for addressing sensitization issues for females as well as males. That is if lifetime exposure to MPH continues to be posited as a risk factor for future substance abuse. It is also of interest that gender washes out of the regression equation as a predictor for MPH overall. It might be speculated that this is because other variables are soaking up the variance from gender. Whether this is the case, or whether boys and girls are converging in their behavior patterns should be investigated.

Moving beyond baseline MPH prescription rates and looking at MPH abuse, the finding that 6.4% of this sample had abused MPH can be fairly easily contrasted with the Monitoring the Future (MTF) study (Bachman, Johnston, & O'Malley, 2001). MTF is administered on a similar scale nationally, and uses instruments similar to the ones used in the current study. Both MTF and ADAS/PPS measures concerned abuse within the last year. The national-based MTF study provides MPH relevant data for years 2001, 2002, and 2003. For the 8^{th} grade, percentages of MPH abuse for those years were 2.9, 2.8, and 2.6 respectively. For the 10^{th} grade they were 4.8, 4.8, and 4.1. And for the 12^{th} grade they were 5.1, 4.0, and 4.0. As can be seen these percentages are both lower than in the current study, but also suggestive in an inconclusive way that MPH abuse does not necessarily increase with age the way that other substances do. In the current study, there are no differences between groups divided by grade on levels of MPH abuse. This suggests that being in grades 9 or 10 make a youth no less likely than one in grades 11 or 12 to abuse MPH. This is a little surprising as one might expect the frequency of this behavior to increase with higher grades.

Highlighting the exceptional nature of these findings, MTF marijuana/hashish rates of abuse in the year 2000 increased from 15.6% in the 8^{th} grade to 32.2% in the 10^{th} grade, and 36.5% in the 12^{th} grade. Thus, it can be seen that marijuana use increases predictably and reliably in the higher grades. A search of MTF reveals that besides MPH, there are no substances that are abused that do not increase this way. This represents a significant finding in that MPH may be an early drug of abuse for many youths. This may or may not represent an atypical route to further drug abuse but MPH abuse and general style of drug use *are* highly correlated in this study. Therefore there should be some concern that early MPH abuse is predictive of the use of other abused substances later on. This too needs to be the subject of further empirical study. As the MPH abuse variable continues to be assessed by MTF over time, a clearer pattern from within their work should begin to emerge. In any case, there is little to suggest at this point in time that these equivalent MPH abuse rates across grade groups in the current study are not representative of the general population. Possible hypotheses for this phenomenon if it proves to be a consistent pattern should include: issues of access of an abusable substance, monitoring of medication, and peer factors.

In relation to the link between MPH and substance abuse generally, it should be reassuring that preliminary analyses in the current study found that a history of MPH prescription is not a predictor of MPH or other substance abuse in and of itself. This should be of some comfort to those who are trying to defend the relative safety and efficacy of these well-established medications. It should be of much greater concern that MPH prescription history interacts so significantly with cigarette smoking to predict MPH abuse. Therefore, it is important to more clearly describe the relationship between MPH and cigarette smoking.

Before looking again at the results of the regression used in the current analyses relevant to discussion of this relationship, it is important to note that in creating the interaction term between MPH prescription history and smoking behaviors, it was found that those with a history of MPH prescription were significantly more likely to smoke than those without that history. While there is also a high correlation between style of drug use and smoking (.56), these are still somewhat discrete predictors as can be seen when we look at the results of the regression. While style of use accounts for the largest share of the (explainable) variance (81.4%) the interaction between *(a positive)* MPH prescription history and smoking is the next most powerful predictor, explaining a relatively substantial 17.1% of unique variance. This becomes interesting when it is remembered that MPH prescription history alone is not predictive of MPH abuse, and that smoking alone explains a mere 1.6% of the variance when the interaction term is included. What are some of the possible explanations for this?

Nicotine may in fact be interacting with ADHD with MPH prescription history serving as a crude proxy for ADHD. An investigation of the literature reveals several things: Milberger, Biederman, Faraone, Chen, and Jones (1997) found that use of nicotine increased the risk of developing a SUD five times for those teenagers with ADHD. Others (Disney et al. 1999) have found main effects for ADHD and nicotine for predicting substance use after controlling for Conduct Disorder. However, contrasting with this, Gittelman, Mannuzza, Shenker, and Bonagura (1985) found that elevated levels of nicotine use for ADHD youth were mediated by the presence of conduct disorder. Possibly finessing this last finding, one well established group of researchers found that ADHD was associated with early initiation of smoking, even after controlling for socio-economic status, IQ, and psychiatric comorbidity. They found this to be *particularly* true for those youths with both ADHD and conduct disorder (Milberger, Biederman, Faraone, Chen, & Jones 1997). Relatedly, Sullivan and Rudnick-Levin (2001) found that nicotine dependence among *adults* with ADHD was substantially more common (40%) than in the general population (26%). Another smoking study found that adolescent ADHD *inattention* symptoms increased the likelihood of current smoking 180% while controlling for peer smoking behavior (Tercyak, Lerman, & Audrain 2002). Supporting the role of ADHD itself increasing smoking behaviors, Burke, Loeber, and Lahey (2001) also found that inattention increased early adolescent risk of smoking by 130% after controlling for CD and other smoking risk factors. Overall, they found a full 51% of their ADHD participants reporting tobacco use.

Thus, ADHD appears to present elevated risks for smoking and consequent substance abuse, with inattentive symptoms indicated as being most involved with driving the smoking behavior. What could account for this increased risk surrounding inattentive symptomology? It was demonstrated by Krause et al. (2002) that nicotine acts much like a stimulant on the brains of those with ADHD. Animal studies (Ueno et al., 2002) support this idea in work that approximates an animal model of ADHD behavior. These researchers show that by alternately providing and then blocking the reception of nicotine molecules they could demonstrate both the mechanism and effectiveness of nicotine in improving the performance of rats on appropriate cognitive tasks. Similarly, cognitive performance in humans has been shown to be improved by a range of stimulant like substances including nicotine (Riccio, Waldrop, Reynolds, & Lowe, 2001).

So, in trying to understand the relationship between MPH and smoking, it appears that nicotine has a significant positive effect on the symptoms of ADHD. In fact, nicotine is now being considered by some as a potential 'non-stimulant' treatment alternative for ADHD (e.g. Biederman, & Spencer, 2000). Nicotine has been shown to improve attentiveness in schizophrenics, with Alzheimers patients, and with those with ADHD. In a preliminary study Levin et al. (1998) investigated whether transdermal nicotine patches would improve attentiveness in non-smoking adults without ADHD. Performance on a Continuous Performance Task was significantly improved both in terms of reaction time and accuracy for these subjects. This author, in a later paper (Levin & Rezvani, 2000) describes the dopaminergic and glutaminergic working memory hippocampal mechanisms that nicotine seems to work upon. Levin puts forward an unequivocal belief in the possibility of safe and effective nicotinic treatments for attentional disorders. This belief is supported by studies using nicotine patches with small groups of adults and adolescents with ADHD. These placebo controlled studies controlled for possible relief from withdrawal effects for smokers, and found significant increases in both CPT performance and in vigor of performance with minimal side effects (Conners et al. 1996; Levin et al. 1996). Levin's most recent work points to the identification of specific nicotinic compounds that may show the most clinical effectiveness (Levin, 2002). Of possible interest too is the suggestion that there exists a synergistic interaction between nicotine and MPH in increasing extracellular dopamine, which in turn may go some way towards further explaining elevated levels of smoking for this group (Gerasimov et al., 2000). However, this does not serve to explain why there are no smoking differences between MPH abusers with a history of prescription and those without. While aggression does not appear to be a significant predictor in the current study, it could be that conduct disordered and aggressive behaviors without ADHD symptomology are a significant predictor for a subset of youth who smoke (Leff et al., 2003).

Ironically, it also appears as though nicotine may alternately play a part in the etiology of ADHD as well being a potential treatment, and a deleterious consequence. Schettler (2001) describes various toxic threats to the neurologic development of children including lead, mercury, alcohol, and nicotine. He postulates a range of problems including learning disabilities, developmental delays, and behavioral problems like ADHD stemming from exposure to these substances. Animal studies have shown hyperactivity in the offspring of nicotine exposed rats (Newman, Shytle, and Sanberg, 1999). Other researchers (Hill, Lowers, Locke-Wellman, & Shen, 2000) have looked at prenatal exposure to alcohol and nicotine in those with ADHD. They found both of these substances to be risk factors for ADHD after controlling for known risk factors like SES and anti-social personality disorder. Another group

(Milberger, Beiderman, Faraone, & Chen, 1996) studied the role of maternal smoking in the etiology of ADHD in boys. They found that 22% of ADHD children had prenatal exposure to nicotine as opposed to 8% of the control subjects. The significance of this association remained even after controlling for SES, parental IQ, and parental ADHD status. They also found significant IQ differences between those children whose mothers smoked and those who did not (mean IQ = 104.9, SD =12.3 and mean = 115.4, SD = 12.2 respectively). These same researchers found that smoking was found to be familial in ADHD but not in control families. In 2002, Mick, Biederman and Faraone went on to show that ADHD cases were 2.1 times more likely than non-ADHD controls to have been exposed to nicotine prenatally after controlling for both conduct disorder and social adversity (Biederman, Faraone, Sayer, & Kleinman, 2002). Overall, there seems to be a compelling case for nicotine contributing to the etiology of a disorder, which ironically (and possibly consequentially) it is then used to (self) medicate. Further reinforcing the intertwined relationship between these substances MPH has been used successfully to treat nicotine withdrawal (Robinson et al. 1995). In sum, it seems plausible that smoking behaviors are driven by somewhat different factors for both the MPH prescribed and the unprescribed groups. Due to the associated risks of smoking for all groups it will be important for researchers to garner a greater understanding of what drives these behaviors in an effort to identify risk factors and implement interventions.

As can be seen in the results chapter, the discriminant analysis was able to successfully discriminate between the three groups using most of the variables hypothesized to be relevant to this study. The first function discriminated between the MPH prescribed non-abusing group and the two other MPH abusing groups (prescribed and non-prescribed). The second function was able to discriminate between the two MPH abusing groups. As previously stated, function one is best characterized by the style of drug use variable and smoking behaviors. The second function is best described by the physical assault on a person variable and gender.

An examination of variable means for each of these groups reveals which groups score higher on the behaviors described by the relevant variables. For function one, the MPH abusing groups are different from the MPH prescribed non-abusing group by their elevated levels of (mainly) other drug use behaviors, but secondarily by their cigarette smoking behavior and gender. It should not be surprising that other illicit drug use is the strongest predictor of MPH abuse across groups, but it should also be considered that there were no grade group differences in rates of MPH abuse. If MPH abuse was purely driven by the use of other substances one would expect to see a concomitant rise in MPH abuse levels as other substances are increasingly abused. So, one has to suppose that either MPH falls out of favor as a drug of abuse or issues of access make it a drug that is abused earlier than many others. As was suggested above, this will be important to determine in relation to prevention efforts.

Those with a history of MPH prescription who did not abuse MPH were less likely to smoke cigarettes than their peers who did abuse, and the MPH abusing group without a history of prescription. This reinforces the notion that nicotine use is associated with elevated risks for substance use in general, but also that it may present as a special risk for MPH abuse for the group with a history of MPH prescription. It also appears that being male is nearly as much of a risk factor for abusing MPH as smoking behaviors. Thus, male adolescents who smoke and abuse other substances are most at risk for abusing MPH. Conversely, female non smokers who do not abuse other substances are least at risk for abusing MPH according to the findings of this study.

Differentiating between the two MPH abusing groups is achieved by the physical aggression against a person variable and by gender. An examination of group means shows that the prescribed/abusing group is more likely to be male and more likely to be aggressive to another person than the non-prescribed/abusing group. Before examining too much further what the reasons for this difference might be, it should be remembered that the factors which discriminate between abusers and non-abusers represent the vast majority of these variables abilities to differentiate between these three groups (96.1% versus 3.9% of the explainable variance). Having said that, this function is still significant, meaning that the abusing groups *are* different from each other. Why then, is the prescribed/abusing group more likely to be aggressive and male? The most likely explanation is that a significant proportion of the prescribed/abusing group has co-morbid ADHD/Conduct Disorder. This is a combination that has been shown to be associated with higher risks of substance abusing behavior and with aggressive behaviors (Barkley, 2003). It may be that for those boys that meet criteria for ADHD who also abuse MPH that this relationship is largely mediated by the presence of a Conduct Disorder (CD), a disorder which is significantly more common in males than in females (American Pyschiatric Association, 1994).

Summary and Conclusions

In summary, this study found that lifetime prevalence of MPH prescription for a nationally derived sample was about 7.4%. This finding is towards the higher end of the spectrum compared to other studies. This figure represents an aggregate derived from regions across the United States and may contain regional variation and differences in prescribing practices. Nonetheless, it is suggestive of an increasingly high number of youths being able to access MPH as a potential drug of abuse. It also appears that there are significant differences in prescription rates by race. While this factor was not a significant predictor of MPH abuse in this case, it may have some relevance in terms of availability of MPH for a given population.

While the lifetime prevalence rates used in this study are hard to compare to the point prevalence rates used in other studies, there may be some utility in this method for studying sensitization issues. To parse this further, future developmental studies should assess onset, intensity and duration of MPH prescription while controlling for behavioral variables.

This study also found a significantly higher ratio of girls to boys prescribed MPH than has previously been estimated. This should serve to emphasize the increasing relevance of gender as a variable in future research.

Abuse of MPH was found at a higher rate than in the MTF studies for approximately the same period. This might suggest that MPH abuse is a more serious problem than has been previously assessed. It was also found that MPH abuse in MTF and in this study did not follow the pattern that all other drugs of abuse show, with substances being abused to a greater degree by youths in higher grades. MPH was not abused any less by the youth in the younger grade group in the current study; a finding which nuances the inconclusive and preliminary date found by MTF. This finding has implications that concern MPH as an early drug of abuse, due to accessibility or other factors. The finding that MPH is being abused by younger kids at the same rate as older kids (who are far more likely to be abusing other substances) should be of serious concern to those who control the supply of this medication. While MPH prescription may not be predictive of future drug abuse, it is not yet known whether early MPH *abuse* will be predictive of future substance abuse problems.

Possibly the most important finding of this study is that the interaction between a history of MPH prescription and smoking is second only to other illicit drug abuse in predicting MPH abuse. This is reinforced by the finding that smoking itself only adds a small amount of explanatory variance to the model. This identification of a conceptually significant risk factor for MPH abuse among those youths who have greatest access to it should serve to focus preventative efforts in the future. This finding also serves to further nuance the complex interwoven relationships between MPH, ADHD, nicotine, and other substance abuse.

The discriminant analysis used was successfully able to differentiate between the three groups using the theoretically derived model. MPH abusing youth were distinguished by their other drug use, smoking and gender. MPH abusers with a history of MPH prescription were different from MPH abusers with no prescription histories by being more likely to be female and more likely to be aggressive to another person. Future studies should examine this finding in relation to ADHD subtypes, Conduct Disorder, and substance abuse.

Limitations of this study that should be noted include the fact that this study was able to explain 13% of the variance in discriminating MPH abusers/non-abusers, leaving a significant proportion of the drivers of MPH abuse unexplained. This study is by necessity correlational leaving many questions about causation unanswered. It was also not possible to break down this analysis by other theoretically significant variables like geographic region, or psychiatric diagnoses.

It should also be noted that this study relies completely upon self-report information. While this does represent a limitation in that there were no corroborative or collateral sources of information available to validate this information, a number of researchers have evidenced the validity of using self report measures with this population. Oetting and Beauvais (1990) documented the validity of self-report substance use measures used in large populations, including the survey materials administered in the present study. Also, O'Malley, Johnson, Bachman and Schulenberg (2000) revealed that there were no significant differences between substance use data collected via anonymous versus confidential methods. A main concern with self-report data focuses on minimizing drug use reporting due to participants' fears of being identified with their answers. As noted above, during the collection of this data rigorous efforts sought to ensure the confidentiality of all of the students participating in this study. Moreover, a series of checks of consistency and exaggerated responses also enhance the overall validity of the data retained for analyses (Oetting and Beauvais (1990).

MPH abuse in a school age population is an understudied area. This preliminary and exploratory study should go some way the construction of a model that describes the relationships between gender, smoking, behavioral problems, MPH abuse, and other substance use in a way that seeks to identify and address the needs of all school age youth who are at risk for abusing substances of all kinds. Implications for prevention and treatment include; carefully monitoring access, administration, and dosing of MPH medication; greater and more focused efforts to prevent smoking behaviors, accompanied by adequate MPH dosing to reduce the need to supplement medication effects by nicotine use; and further examination of both the role of early MPH abuse as a predictor of later substance abuse, and the role of nicotine as a moderator or mediator of that process. It may be that while stimulant medication has a protective effect against substance use disorders for ADHD youth, this effect is significantly compromised by smoking behaviors, which ADHD youth in particular are at greater risk for. Longitudinal studies would go a great way towards answering this question. It can only be hoped that this exploratory study provides some direction for other researchers to comprehensively address these conceptual issues in studies of early adolescent substance abuse and psychiatric co-morbidity.

REFERENCES

Achat-Mendes, C., Anderson, K.L., & Itzhak, Y. (2003) Methylphenidate and MDMA adolescent exposure in mice: Long lasting consequences on cocaine-induced reward and psychomotor stimulation in adulthood. Neuropharmocology 45, 106-115

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition. Washington DC: American Psychiatric Association.

Aiken, Leona S; West, Stephen G. (1991). Multiple regression: Testing and interpreting interactions. Thousand Oaks, CA, US: Sage Publications, Inc.

Anderson, S. L., Arvantogiannis, A., Pliakas, A. M., LeBlanc, C. &Carlezon, W. A., Jr. (2002). Altered responsiveness to cocaine in rats exposed to methylphenidate during development. Natural Neuroscience, 5, 13-14.

Babcock, Q., & Byrne T. (2000). Student perceptions of methylphenidate abuse at a public liberal arts college. Journal of American College Health, 49, 143-145.

Bachman, J. G., Johnston, L. D., O'Malley, P. M. (2001). The Monitoring the Future project after 27 years: Designs and procedures. Monitoring the Future Occasional Paper No. 53. Ann arbor, MI: Institute for Social Research.

Barkley, R. A. (1990). Attention Deficit Hyperactivity Disorder. NY: Guilford.

Barkley, R. A. (2003). Does stimulant medication therapy for ADHD in children predispose to later drug use? The ADHD Report, 11 (1), 2-7.

Barratt, S. P., & Pihl, R. O. (2002). Oral methylphenidate-alcohol co-abuse. Journal of Clinical Psychopharmacology, 22, 633-634.

Biederman, J. (2003). Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: findings from a longitudinal follow-up of youths with and without ADHD. Journal of Clinical Psychiatry, 64, 3-8.

Beiderman, J., Wilens, T., Mick, E., Spenser, T. & Faraone, S. V. (1999). Pharmacotherapy of Attention Deficit Hyperactivity Disorder reduces risk for substance use disorder. Pediatrics, 104, 20.

Biederman J, Spencer T. (2000). Non-stimulant treatments for ADHD European Child and Adolescent Psychiatry, 9, 51-59.

Bonate, P. L., Swann, A. C. & Silverman, P.B. (1997). Context dependent cross sensitization between cocaine and amphetamine. Life Sciences, 60, 651-661.

Brandon, C. L., Marinelli, M., Baker, L. K. & White, F. J. (2001). Enhanced reactivity and vulnerability to cocaine following methylphenidate treatment in adolescent rats. Neuropsychopharmacology, 25, 651-661.

Brandon, C. L. & Steiner, H. (2003). Repeated methylphenidate treatment in adolescent rats alters gene regulation in the striatum. European Journal of neuroscience, 18, 1584-1592.

Burke, J. D., Loeber, R., & Lahey, B.B. (2001). Which aspects of ADHD are associated with tobacco use in early adolescence? Journal of Child Psychology and Psychiatry, 42, 493-502.

Chait, L. D. (1994). Reinforcing and subjective effects of methylphenidate in humans. Behavioural Pharmacology, 5, 291-288.

Coger, Roger W., Moe, Kathryn L., Serafetinides, E. A. Attention deficit disorder in adults and nicotine dependence: Psychobiological factors in resistance to recovery? Journal of Psychoactive Drugs, 28, 229-240.

Cohen, J., & Cohen, P. (1983). Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences (2nd Ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Conacher, G.N. (1997). Pharmacological Approaches to Impulsive and Aggressive Behavior. In Webster, C.D., & Jackson, M.A. (Eds.), Impulsivity: Theory, Assessment, and Treatment. New York: Guilford.

Conners, CKeith; Levin, Edward D; Sparrow, Elizabeth; Hinton, Sean C. (1996). Nicotine and attention in adult attention deficit hyperactivity disorder (ADHD). Psychopharmacology Bulletin, 32, 67-73.

Cox, E.R., Motheral, B.R., Hendrson, R.R., & Mager, D. (2003). Geographic variation of stimulant medication use among children 5-14 years old: Results from a commercially insured US sample. Pediatrics, 111, 237-243.

Deffenbacher, J.L., & Swaim, R.C. (1999). Anger expression in Mexican American and White non-Hispanics adolescents. Journal of Counseling Psychology, 46, 61-69.

Disney, E.R., Elkins, I.J., McGue, M., and Iacono, W.G. (1999). Effects of ADHD, Conduct Disorder, and Gender on Substance Use and Abuse in Adolescence. American Journal of Psychiatry, 156, 1515-1521.

Drug Enforcement Administration (1997). Conference Report: Stimulants Used in the Treatment of ADHD. Washington DC: Office of Diversion Control.

Ellinwood, E. H. & Lee, T. H. (1989). Dose and time dependent effects of stimulants. National Institute of Drug Abuse monograph no. 94, 323-40.

Faraone, S. V., & Wilens, T. (2003). Does stimulant treatment lead to substance use disorders? Journal of Clinical Psychiatry, 64, 9-13.

Fisher, B. C. (1998). Attention Deficit Disorder Misdiagnosis: Approaching ADD from a Brain-Behavior/Neuropsychological Perspective for Assessment and Treatment. Boca Raton FL: CRC.

Fischer, M., & Barkley, R. A. (2003). Childhood stimulant treatment and risk for later substance abuse. Journal of Clinical Psychiatry, 64, 19-23.

Foley, R., Mrvos, R., & Krenzelok, E. P. (2000). A profile of methylphenidate exposures. Journal of Toxicology and Clinical Toxicology, 38, 625-630.

Garland, E. J. (1998). Intranasal abuse of prescribed methylphenidate. Journal of the American Academy of Child and Adolescent Psychiatry, 37, 573-4.

Gatley, S. J., Volkow, N. D., Gifford, A. N., Fowler, J. S., Dewey, S. L., Ding, Y. S. & Logan, J. (1999). Dopamine transporter occupancy after intravenous doses of cocaine and methylphenidate in mice and humans. Psychopharmacology, 146, 93-100.

Gerasimov, M. R., Franceschi, M., Volkow, N. D., Gifford, A., Gatley, S. J., Marsteller, D., Molina, P. E., Dewey, S. L. (2000). Comparison between intraperitoneal and oral methylphenidate administration: A microdialysis and locomotor activity study. Journal of Pharmacology & Experimental Therapeutics, 295, 51-57.

Gittelman, R.S., Mannuzza, R.S., Shenker, R., & Bonagura, N. (1985). Hyperactive boys almost grown up. Archives of General Psychiatry, 42, 937-947.

Glantz, M. D., Weinberg, N. Z., Miner, L. L.,& Colliver, J. D. (1999). The Etiology of Drug Abuse: Mapping the Paths. In M. D. Glantz & C. R. Hartel (Eds.), Drug Abuse: Origins and Interventions. Washington, DC: American Psychological Association.

Goldstein, S., & Goldstein, M. (1998). Managing Attention Hyperactivity Disorder in Children: A Guide for Practitioners. Second Edition. NY: Wiley.

Graff-Low, K., & Gendaszek, A. E. (2002). Illicit use of psychostimulants among college students: a preliminary study. Psychology, Health, and Medicine, 7, 283-287.

Grimm, Laurence G [Ed]; Yarnold, Paul R [Ed]. (1995). Reading and understanding multivariate statistics. Washington, DC, US: American Psychological Association.

Haglund, M. J., & Howerton, L. L. (1982). Ritalin: consequences of abuse in a clinical population. The International Journal of the Addictions, 17, 349-356.

Hill, S. Y., Lowers, L., Locke-Wellman, J., Shen, S. Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. Journal of Studies on Alcohol, 61, 661-668.

Horger, B. A., Giles M. K., & Schenk, S. (1992). Pre-exposure to amphetamine and nicotine predisposes rats to self administer a low dose of cocaine. Psychopharmacology, 107, 271-276.

Huberty, Carl J. Why multivariable analyses? (1994). Educational & Psychological Measurement, 54, 620-627.

Huss, M. & Lehmkuhl, U. (2002). Methylphenidate and substance abuse: a review of pharmacology, animal and clinical studies. Journal of Attention Disorders, 6, 65-71.

Ittenbach, R. F., Bruininks, R. H. Thurlow, M.L., & McGrew, K. S. (1993). Community integration of young adults with mental retardation- a multivariate-analysis of adjustment. Research in Developmental Disabilities, 14, 275-290.

Jaffe, S. L. (1991). Intranasal abuse of prescribed methylphenidate by an alchol and drug abusing adolescent with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry, 30, 773-775.

Klein, R. G., & Mannuza, S. (2002). Stimulant sensitization in children. Journal of Attention Disorders, 6, 61-64.

Klein-Schwartz, W., and McGrath, J. (2003). Poison center's experience with methylphenidate abuse in pre-teens and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry, 42, 288-294.

Klein-Schwartz, W. (2002). Abuse and toxicity of methylphenidate. Current Opinions in Pediatrics, 14, 219-223.

Kollins, S. H., MacDonald, E. K. & Rush, C. R. (2001). Assessing the abuse potential of methylphenidate in nonhuman and human subjects-A review. Pharmacology, Biochemistry and Behavior, 68, 611-627.

Kollins, S. H. (2003). Comparing the abuse potential of methylphenidate versus other stimulants: a review of available evidence and relevance to the ADHD patient. Journal of Clinical Psychiatry, 64, 14-18.

Krause KH, Dresel SH, Krause J. (2002). Stimulant-like action of nicotine on striatal dopamine transporter in the brain of adults with attention deficit hyperactivity disorder. International Journal of Neuropsychopharmacology, 5, 111-113.

Kuczenski, R., & Segal, D. S. (1997). Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: Comparison with amphetamine. Journal of Neurochemistry, 68, 2032-37.

Lambert, N. M., & Hartsough, C. S. (1998). Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. Journal of Learning Disabilities, 31, 533-544.

LeFever, G. B., Dawson, K. V., & Morrow, A. L. (1997). The extent of of Drug therapy for ADHD among children in public schools. American Journal Public Health, 89, 1359-1364.

Leff, M. K., Moochan, E. T., Cookus, B. A., Bridget, A., Spurgeon, L., Evans, L. A., London, E. D., Edythe, D., Kimes, A., Schroeder, J. R., & Ernst, M. (2003). Predictors of smoking initiation among high risk youth: A controlled study. Journal of Child and adolescent Substance Abuse, 13, 59-76.

Levin E. D., Conners C. K., Silva D., Hinton S. C., Meck W. H., March J., Rose J.E. (1998) Transdermal nicotine effects on attention. Psychopharmacology, 140, 135-141.

Levin, E. D., Conners, C. K., Sparrow, E., Hinton, S. C., Erhardt, D., Meck, W. H., Rose, J. E., March, J. (1996). Nicotine effects on adults with attention-deficit/hyperactivity disorder. Psychopharmacology, 123, 55-63.

Levin, E. D., Rezvani A. H. (2000). Development of nicotinic drug therapy for cognitive disorders. European Journal of Pharmacology, 393, 141-146.

Levin, E. D. (2002). Nicotinic receptor subtypes and cognitive function. Journal of Neurobiology, 53, 633-640.

Loney, J., Kramer, J. R., & Salisbury, H. (2002). Medicated versus ummedicated ADHD children: Adult involvement with legal and illegal drugs. In P. S. Jensen, & J. R. Cooper (Eds.), Diagnosis and treatment of Attention Deficit Hyperactivity Disorder: An evidence based approach. New York: American Medical Association Press.

Maletzky, B.M. (1976). The diagnosis of pathological intoxication. Journal of Studies on Alcohol, 37, 1215-1228.

Mannuzza S., Klein, R. G., Moulton, J.L. (2003). Does stimulant treatment place children at risk for adult substance abuse? A controlled, prospective follow-up study. Journal of child and Adolescent Psychopharmacology, 13, 273-282.

Markowitz, J. S., Devane, C. L., Boulton, D. W., Nahas, Z., Risch, S. C., Diamond, F., & Patrick, K. S. (2000). Ethylphenidate formation in human subjects after the administration of a single dose of methylphenidate and ethanaol. Drug Metabolism and Disposition, 28, 620-624.

Markowitz J. S., Logan, B. K., Diamond, F. & Patrick, K.S. (1999). Detection of the novel metabolite ethylphenidate after overdose with alcohol co-ingestion. Journal of Clinical Psychopharmacology, 19, 362-66.

Massello, W., & Carpenter, D. A. (1999). A fatality due to the intranasal abuse of methylphenidate (Ritalin). Journal of Forensic Science, 44, 220-221.

McDougall, S. A, Collins, R. L., Karper, P. E., Watson, J. B. & Crawford C. A. (1999). Effects of repeated methylphenidate in the young rat: sensitization to both locomotor activity and stereotyped sniffing. Experimental and Clinical Psychopharmacology, 7, 208-218.

Mercugliano, M. M., Power, T. J., & Blum, N. J. (1999). The Clinician's Practical Guide to Attention Deficit/Hyperactivity Disorder. Maryland: Brookes.

Mick, E., Biederman, J., Faraone, S. V., Sayer, J., Kleinman, S. (2002). Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use and drug use during pregnancy. Journal of the American Academy of Child & Adolescent Psychiatry, 41, 378-385.

Milberger, S., Biederman, J., Faraone, S.V., Chen, L., and Jones, J. (1997). ADHD is associated with early initiation of cigarette smoking in children and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry, 36, 37-44.

Musser, C. J., Ahmann, P.A., Theye, F. W., Mundt, P., Broste, S. K., and Mueller-Rizner, N. (1998). Stimulant abuse and the potential for abuse in Wisconsin as reported by school administrators and longitudinally followed children. Developmental and behavioral Pediatrics, 19, 187-192.

Newman, MB; Shytle, RD; Sanberg, PR. (1999). Locomotor behavioral effects of prenatal and postnatal nicotine exposure in rat offspring. Behavioural Pharmacology, 10, 699-706.

Oetting, E.R., & Beauvais, F. (1990). Adolescent drug use: Findings of national and local surveys. Journal of Consulting and Clinical Psychology, 58, 385-394.

Oetting, E.R., Beauvais, F., & Edwards, R.W. (1985). The American drug and alcohol survey. Ft. Collins, CO: Rocky Mountain Behavioral Science Institute, Inc.

Parran, T. V., & Jasinski, D. R. (1991). Intravenous methylphenidate abuse. Archives of Internal Medicine, 151, 781-783.

O'Malley, P.M., Johnson, L.D., Bachman, J.G., & Schulenberg, J. (2000). A comparison of confidential versus anonymous survey procedures: Effects on reporting of drug use and related attitudes and beliefs in a national study of students. Journal of Drug Issues, *30*, 35-54.

Raskind, M., and Bradford, T. (1973). Methylphenidate (Ritalin) abuse and methadone maintenance. Diseases of the Nervous System, January 1975, 36, 9-12.

Riccio, Cynthia A; Waldrop, Jennifer JM; Reynolds, Cecil R; Lowe, Patricia. (2001). Effects of stimulants on the continuous performance test (CPT): Implications for CPT use and interpretation. Journal of Neuropsychiatry & Clinical Neurosciences, 13, 326-335.

Robinson, M. D., Anastasio, G. D., Little, J. M., Sigmon, J. L. Jr., Menscer, D., Pettice, Y. J., & Norton, J. H. (1995). Ritalin for nicotine withdrawal: Nesbitt's paradox revisited. Addictive Behaviors, 20, 481-490.

Robbins, T. W. (2002). ADHD and addiction. Nature Medicine, 8, 24-25

Rushton, J.L., Whitmire, J. T. (2001). Pediatric stimulant and selective serotonin reuptake inhibitor prescription trends - 1992 to 1998. Archives of Pediatrics and Adolescent Medicine, 155, 560-565.

Sabatino, D. A., & Vance, H. B. (1994). Is the diagnosis of ADHD meaningful? Psychology in the Schools, 31, 188-196.

Safer, D.J., Zito, J.M., & Fine, E.M. (1996). Increased methylphenidate usage for attention deficit disorder in the 1990s. Pediatrics, 98, 1084-1088.

Safer, D. G., & Zito, J. M. (2000). Pharmacoepidemiology of Methylphenidate and Other Stimulants for the Treatment of Attention Deficit Hyperactivity Disorder. In L. L. Greenhill & B. B. Osman (Eds.), Ritalin: Theory and Practice. Second Edition. New York: Mary Ann Liebert.

Safer, D. J., Zito, J. M., and Gardner, J. F. (2004). Comparative prevalence of psychotropic medications among youths enrolled in the SCHIP and privately insured youths. Psychiatric Services, 55, 1049-1051.

Safer, D. J., Zito, J. M. (1998). Letter to the Editor. Journal of the American Academy of Adolescent Psychiatry, 37, 1242.

Sannerud, C., & Feussner, G. (2000). Is Ritalin an abused Drug? Does It Meet the Criteria of a Schedule II Substance? In L. L. Greenhill & B. B. Osman (Eds.), Ritalin: Theory and Practice. Second Edition. New York: Mary Ann Liebert.

Schenk, S., Valadez, A., Horger, B. A., Snow S. & Wellman, P. J. (1994). Interactions between caffeine and cocaine in tests of self-administration. Behavioral Pharmacology, 5, 153-158.

Schenk, S. & Davidson, E. S. (1998). Stimulant pre-exposure sensitizes rats and humans to the rewarding effects of cocaine. NIDA Research Monograph, 169, 56-82.

Statsoft. (2004). Discriminant Analysis.www.Statsoft.com.

Stein, J., Schettler, T., Wallinga, D., Valenti, M. (2002). In harm's way: Toxic threats to child development. Journal of Developmental & Behavioral Pediatrics, 23, S13-S22.

Stoops, W. W., Glaser, P. E. A., & Rush, C. R. (2003). Reinforcing, subject related, and physiological effects of intranasal methylphenidate in humans: a dose-response analysis. Drug and Alcohol Dependence, 71, 179-186.

Sullivan M. A., Rudnik-Levin, F. (2001). Attention deficit/hyperactivity disorder and substance abuse - Diagnostic and therapeutic considerations. Annals of the New York Academy of Sciences, 931, 251-270.

Taylor, E., Sandberg, S., Thorley, G., & Giles, S. (1991). The epidemiology of childhood hyperactivity. New York: Oxford University Press.

Tercyak K. P., Lerman C., Audrain J. (2002). Association of attention-deficit/hyperactivity disorder symptoms with levels of cigarette smoking in a community sample of adolescents. Journal of the American Academy of Child and Adolescent. Psychiatry, 41, 799–805.

Teter, C. J., McCabe, S. E., Boyd, C. J., & Guthrie, S. K. (2003). Illicit methylphenidate use in an undergraduate student sample: prevalence and risk factors. Pharmacotherapy, 23, 609-617.

Ueno, K., Togashi., H., Matsumoto, M., Ohashi, S., Saito, H., & Yoshioka, M. (2002). Alpha 4 beta 2 nicotinic acetylcholine receptor activation ameliorates impairment of spontaneous alternation behavior in stroke-prone spontaneously hypertensive rats, an animal model of attention deficit hyperactivity disorder. Journal of Pharmacology and Experimental Therapeutics, 302, 95-100.

Volavka, J. (1995). Neurobiology of Violence. Washington DC: American Psychiatric Press.

Volavka, J., & Citrome, L. (1998). Aggression, Alcohol, and other Substances of Abuse. In M. Maes & E.F. Coccaro (Eds.) Neurobiology and Clinical Views on Aggression and Impulsivity. New York: Wiley.

Volkow, N. D., Ding, Y., fowler, J.S., Wang, G., Logan, J., Gatley, J. S., Dewey, S., Ashby, C., Liebermann, J., Hitzmann, R., & Wolf, A. P. (1995). Is methylphenidate like cocaine? Archives of General Psychiatry, 52, 456-463.

Wampold, B. E., & Freund, R. D. (1987). Use of multiple regression in counseling psychology research-a flexible data-analytic strategy. Journal of counseling Psychology, 34, 372-382.

Weaver, M. F., & Schnoll S. H. (1999). Stimulants: Amphetamines and cocaine. In McCrady, B. S. & Epstein, E. (Ed.s), Addictions: A Comprehensive Guidebook. (pp. 105-120). New York: Oxford University Press.

Whalen, C. K. (1983). Hyperactivity, Learning Problems, and the Attention Deficit Disorders. In T.H. Ollendick and M. Hersen (Eds.), Handbook of Child Psychopathology. New York: Plenum.

Yang, P. A., Swann, A. C. & Dafney, N., (2003). Chronic pretreatment with methylphenidate induces cross sensitization with amphetamine. Life Sciences, 73, 2899-2911.

Zito, J. M., Safer, D. J., dosReis, S., magder, L. S., & Riddle, M.A. (1997). Methylphenidate patterns among Medicaid youths. Psychopharmacology Bulletin, 33, 143-147.

Table 1

Intercorrelations Between Subscales for Students Grades 9-12

Students (n = 17,000)

Subscale	1	2	3	4	5	6	7	8	9	10	11
1. PAO	1.0	.61**	.67**	.01	-.01	.12**	-.12**	.23**	.16**	.25**	.15**
2. PAP	.61**	1.0	.52**	.25**	-.25**	.17**	-.17**	.30**	.24**	.29**	.23**
3. VA	.67**	.52**	1.0	0	0	.09**	-.09**	.32**	.14**	.30**	.13**
4. Male	.01	.25**	0	1.0	-1**	.12**	-.12**	.08**	.07**	-.01	.10**
5. Female	-.01	-.25**	0	-1**	1.0	-.12**	.12**	-.08**	-.07**	.01	-.10**
6. Rx MPH	.12**	.17**	.09**	.12**	-.12**	1.0	-1**	.10**	.24**	.15**	.84**
7. No Rx MPH	-.14**	-.17**	-.09**	-.12**	.12**	-1**	1.0	-.10**	-.24**	-.15**	-.84**
8. Style	.23**	.30**	.32**	.08**	-.08**	.10**	-.10**	1.0	.32**	.56**	.17**
9. MPH Abuse	.16**	.24**	.14**	.07**	-.07**	.24**	-.24**	.32**	1.0	.30**	.34**
10. Smoke	.25**	.29**	.30**	-.01	.01	.15**	-.15	.56**	.30**	1.0	.32**
11. Int 1	.15**	.23**	.13**	.10**	-.10**	.84**	-.84**	.17**	.34**	.32**	1.0

Note: Correlations less than 0.1 are considered non-significant due to the large sample size
PAO=Physical Aggression against an Object
PAP= Physical Aggression against a Person
VA=Verbal Aggression
Rx MPH=Prescribed Methylphenidate
No Rx MPH=Not Prescribed Methylphenidate
Style=Style of Drug Use
MPH Abuse= Methylphenidate Abuse
Smoke=Cigarette Smoking
Int 1=Interaction between MPH Rx and Smoke

Table 2

Post-Hoc Regression for Smoking on MPH Prescribed and Non-Prescribed Groups

	R	R Square	Adjusted R Square	Std. Error of the Estimate
Smoking for the non-prescribed group	.249	.062	.062	.492
Smoking for the prescribed group	.431	.186	.185	1.286

Table 3

*Final Step of the Multiple Regression Analysis**

		Standardized Beta	S.E.	Sig.
Step 5	Style	.267	.000	.000
	Smoke x MPH Rx	.139	.006	.000
	Smoke	.048	.004	.000
	PAP	.038	.001	.000
	VA	-.022	.001	.026

**Dependent variable: used MPH to get high in last 12 months*

Table 4

Variance Explained Stepwise in Multiple Regression Model

Step	R Square Change	% of variance added	Sig. F Change
1.	.105	81.4	.000
2.	.022	17.1	.000
3.	.002	1.6	.000
4.	.001	0.8	.001
5.	.000	0.0	.026

Note: *Variables entered on Step 1: (Constant), Style of use*
Variables entered on Step 2: (Constant), Style of use, Interaction
Variables entered on Step 3: (Constant), Style of use, Interaction, Smoking
Variables entered on Step 4: (Constant), Style of use, Interaction, Smoking, PAP
Variables entered on Step 5: (Constant), Style of use, Interaction, Smoking, PAP, VA

Table 5

Summary of Canonical Discriminant Functions

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	.521	96.1	96.1	.585
2	.021	3.9	100.0	.145

Table 6

Standardized Canonical Discriminant Function Coefficients

	Function 1	Function 2
Gender	.24	-.61
Smoke	.26	-.09
PAP	-.04	.72
Style	.86	.02

Table 7

Structure Matrix

	Function 1	Function 2
Style	.94*	.21
Smoke	.62*	.06
PAP	.21	.79*
Gender	.19	-.71*
PAO	.25	.39*
VA[a]	.29	.32*

**Largest within-groups correlations between discriminating variables and standardized canonical discriminant functions*

[a] *This variable not used in the analysis*

Table 8

Wilks Lambda

Test of function(s)	Wilks Lambda	Chi-square	df	Sig.
1 through 2	.64	566.31	8	.00
2	.98	27.195	3	.00

Table 9

Group Statistics

Prescription/Abuse Category		Mean	Std. Deviation
Prescribed, Didn't Abuse	Gender	1.31	0.51
	Smoke	1.90	1.19
	VA	11.71	3.45
	PAO	9.87	3.56
	PAP	7.23	3.46
	Style	8.67	8.96
Not Prescribed, Abused	Gender	1.49	0.53
	Smoke	3.04	1.34
	VA	13.31	2.81
	PAO	10.84	3.54
	PAP	8.08	3.71
	Style	21.67	10.11
Prescribed, Abused	Gender	1.30	0.49
	Smoke	2.96	1.36
	VA	13.28	3.18
	PAO	11.32	3.80
	PAP	9.36	4.13
	Style	21.32	10.25
Total	Gender	1.38	0.52
	Smoke	2.45	1.38
	VA	12.49	3.29
	PAO	10.40	3.62
	PAP	7.80	3.70
	Style	15.02	11.53