Examining Tolerance to CNS Stimulants in ADHD

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Importance

ADHD is one of the most recognized and treated psychiatric disorders of childhood (ADHD). A population survey in 2007-2008 of 4-17 year old children in the USA estimated that 9.5% (about 5.4 million) had received a diagnosis of ADHD and 4.8% (2.7 million) were in current treatment with stimulant medications, typically methylphenidate and amphetamine (Vissers et al., 2010). A massive literature exists on the short-term effects of stimulant medication (see Swanson et al., 1993 for an early "review of reviews", and an update provide a decade later by Conner, 2003). Despite the widespread use of stimulant medications that have robust acute effects, the long-term outcomes for many ADHD are disappointing at best. This point is emphasized in the recently released AAP guidelines for ADHD that state the ability to "achieve long term successful outcomes still remain a challenge" (AAP, 2011 pg 13). While, the literature on long-term effects is sparse, that which exists routinely fails to detect appreciable effects of treatment (Barberesi et al., 2007 Marcus et al., 2007 Scheffler et al., 2009). A recent review on the long term effects of stimulant medication concluded that the existing studies fail to clearly demonstrate long term benefits (Hazell, 2011). The Multimodal Treatment Study of ADHD (MTA), which is the largest and most widely cited longitudinal treatment study of ADHD to date (MTA, 1999), provides a painfully clear illustration of this effect. In it, state-of-the-art treatment with or without stimulant medication was provided at a relatively young age (7 to 9 years). At the end of a 14-month treatment-by-protocol phase, all of the assigned treatment groups showed substantial improvement, but the assigned treatment conditions with stimulant medication as a component (Med and Comb) were superior to the treatment condition without stimulant medication as a component (Beh). However, during the naturalistic follow-up phase of the MTA, the relative superiority of assigned pharmacological over non-pharmacological treatment dissipated by 50% by the 24-month assessment (MTA Group, 2004) and completely by the 36-month assessment (see Jensen et al., 2007). Even MTA subjects with a decade of medication usage did not exhibit improved long term outcomes, suggesting that nonadherence, while common (Marcus, 2005, 2011), is not the primary cause of the lack of sustained benefit (Molina et al., 2009).

Another possible explanation for the failure of chronic medication usage to alter long term outcomes is the development of tolerance. Tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in a decrease of the drug's effects over time (Dupen, Shen & Esrek 2007). There are two ways to maintain full effects despite the presence of tolerance: (1) escalating dose of the drug over time as tolerance emerges (2) interrupting dosing to allow tolerance to dissipate before given the next dose. Concerns about possible tolerance to the therapeutic effects of stimulants data back over 30 years. For example in 1975, Safer and Allen reported diminishing behavioral responses after the first year of treatment with methylphenidate. Similar results have been reported for the cognitive effects of methylphenidate (Richardson, 1988) with decaying efficacy noticed within three months of use. The hypothesis of long-term tolerance (defined here as occurring after the medication has cleared the body to distinguish from acute tolerance or tachyphylaxis) was formally proposed by Swanson 25 years ago (Swanson, 1986). Here, it was observed in a clinical practice setting, that aggressive escalation of dose of MPH to extremely high doses (e.g., 100 mg 4 times a day) was required to maintain full therapeutic effect. Surprisingly, no appreciable worsening in acute tolerability was noted. More recently, in the NIH funded Preschool ADHD Treatment Study (PATS) Wigal et al (2007) documented the dissipation of some side effects even when dose increases occur.

Tolerance has been demonstrated to occur in a variety of other CNS agents from analgesics to anticonvulsants (Abou-Khalil & Lazenby 2003; Ossipov et al., 2005). It is not uncommon to have to switch to an alternate anticonvulsants or opioids after chronic exposure in order to recapture lost effect (Kloke et al., 2000; Zhang et al., 2003). In fact, tolerance to opioid based analgesics is an extremely well documented phenomena that has been the source of extensive research (Dupen, Shen & Esrek 2007). The presence of tolerance across multiple classes of drugs suggests that tolerance may be more related to properties of the medications themselves then the diseases they target. Therefore, it is difficult to understand why tolerance would not occur to stimulants in the clinical treatment of ADHD.

Investigations into one aspect of tolerance to CNS stimulants has already led to a dramatic shift in the treatment paradigms for ADHD. Before the innovative concept of acute tolerance (or tachyphylaxis) was tested, the consensus was that a flat or descending PK profile is desirable for stimulant medication. This effect was routinely achieved by using lower afternoon than morning doses of an immediate release (IR) stimulant, including in the MTA (Greenhill, 2001). However, this practice assumes that tachyphylaxis does not occur, so that a constant drug level would maintain full effect. Based on the principles of pharmacology and the pharmacokinetic/pharmacodynamics (PK/PD) properties of stimulant drugs, a translational approach was taken to gain theoretical understanding of the reduced efficacy of first-generation controlled-release formulations of

stimulant medications (i.e., Ritalin SR®). The key to these proof-of-concept studies was the use of a sensitive surrogate measure of the pharmacodynamic (PD) response in an analog classroom setting, namely the 10 minute timed math test (MMT). *The 10-MMT has been widely used to document the efficacy of novel stimulant formulations (Greenhill et al., 2003; McCracken et al., 2003; Swanson et al., 2004) and is accepted by the FDA as a surrogate measure of magnitude of efficacy (Swanson, 2002). The effect size in the above studies for the objective the 10-minute math test has been large (e.g., about 1.0) and equal to or larger than that for more subjective parent and teacher completed rating scales.* The results – loss of full effect with a flat profile and achievement of full effect with an ascending profile -- led to the use of ascending profiles in the design of second generation controlled-release formulations (OROS MPH: Pelham et al., 2001 Swanson et al., 2000/2003)) and amphetamine (Adderall XR®: Greenhill et al., 2003; McCracken et al., 2005; McGough et al., 2003). These new products were almost immediately adopted and have remained the standard of care for ADHD (Pliszka, 2007).

In addition to clinical experience with stimulants, recent advancements in neuroscience surrounding the proposed therapeutic mechanisms of these agents for ADHD suggest that long-term tolerance may in fact occur with therapeutic use of stimulants. The primary neural target of methylphenidate is the dopamine transporter (DAT), which has a high density in the striatal brain regions. Wang et al (2009) and Volkow et al (2009) documented increased density of DAT after a year of clinical treatment. A recent meta-analysis found a strong association between prior stimulant exposure and DAT density (Fusar-Poli, et al., 2011). Based on this finding, the authors theorized that increasing DAT density may be an adaptive CNS response to long term stimulant usage that could explain the limited capacity of stimulants to impact the long term functioning of patients with ADHD. Hence, there is now a data driven model supporting the development of tolerance to the therapeutic effects CNS stimulants on ADHD symptoms.

The few studies that have discounted the existence of examined long term tolerance were essentially naturalistic follow-up studies with significant methodological limitations. For example, Safer and Allen (1989) examined tolerance using a chart review of youth who had experienced a 50% or greater reduction in symptoms during the first three years of treatment. They focused on the subsequent two years of treatment (years 4 and 5), assuming that tolerance would be most likely to occur years after optimal dose was achieved. Since no significant increase in dose was seen in years 4 and 5, it was concluded that tolerance did not occur. However, subjects who could not be maintained on a stable dose for more than two years were excluded, yet this would be the group most likely to be experiencing tolerance. Moreover, the vast majority of these youth were taking short acting MPH on school days only, so the naturally occurring drug holidays on weekends and summer vacations may have precluded the development of tolerance. Hence, this study established ONLY that tolerance does not routinely occur years after the dose is optimized, suggesting that examinations of tolerance should occur earlier in the treatment course.

The report detailing the results of the 14-month medication algorithm of the MTA also raises the possibility of tolerance to clinical doses of stimulants over a school year (Vitiello et al, 2001). There were appreciable changes in dose that are consistent with the development of tolerance. An initial placebo-controlled, double-blind, dose-response 30-day trial on methylphenidate (MPH) documented large initial beneficial effects of MPH (Greenhill, 2001). This phase was followed by 13 months of systematic, study-based medication monitoring. In monthly clinic visits, protocol-driven dose adjustments were made to maintain full effectiveness based on review of collected efficacy (teacher, parent, therapist) and safety (side effect) ratings. The dosing patterns of the Medication Only group may be most relevant as the concomitant provision of intensive behavioral services has been found to reduce the need for dose adjustments (Pelham et al., 2005; Vitiello et al., 2001). In the MTA maintenance phase, a dose increase was required in 54% of the participants in the medication only arm. The mean dose in the Med group increased 18% from 32.2mg to 38.1mg, while the mg dose per kg of body weight increased 19% from 1mg/kg/day to 1.19mg/kg. By the end of randomized treatment phase the Med group had a higher absolute dose ($p<.001$) and weight based dose ($p<.01$) than the Comb group despite starting out a comparable doses (Vitiello et al., 2001; Fig. 2 below). The mean time to first change was 4.1 months with average of 2.76 changes over the duration of the randomized treatment phase. *The presence of ODD/CD or other allowable comorbidities did not impact mean dose or time to dose change. Gender impacted mean dose but not time to dose change.* As there were 13 opportunities to change dose over the RCT phase, this means that a dose change occurred at 21% of the possible times. This estimate is conservative as not all outcome assessments were available at each visit nor did every visit occur as scheduled, so the absence of a symptom change was likely interpreted as sustained efficacy. Hence, even though medication led to sustained effects over the first year of treatment in the MTA, it was achieved by

incrementally increasing the dose, an increase in which was needed per repeated assessment, even though the optimal dose had been previously determined under placebo controlled settings. The regression line in figure 2 suggests that the dose of stimulant will have to be increased by 18% per year to maintain the initial effect. Although we cannot be certain that tolerance is responsible for this need for increasing dose and there are alternative explanations (Vitiello et al, 2001), tolerance is a parsimonious explanation that warrants further research. If the increases in dose over time in a natural setting could be linked to laboratory-based, controlled evaluations of tolerance, a stronger argument that tolerance might explain the dose escalations needed in the natural environment.

One obvious argument against tolerance is that dose increases over time may be associated with the physical growth in developing children. In the medication only group the dose increased from 32.2 to 38.1 mg/day for one year increase of **5.9mg**. Over this time period, the med group gained **1.91 kilos** for a ratio of **3.1 mg** of medication for every kilo of body weight gained which is well above standard dosing norms of 1mg/kg/day of body weight (Greenhill, 2003). Moreover, Safer & Allen (1989) found that using mg of MPH/kg of body weight overestimates the predicted dose increase needed to correct for growth; therefore, the observed discrepancy between actual dose increase and expected dose increase due to growth is likely larger than what was observed. Furthermore, Swanson et al (1978) reported that in children, a 6-fold difference exists between clinically optimal dosages across individuals that was unrelated to weight. Hence, there is not always a need to increase dose simply based on increased body mass.

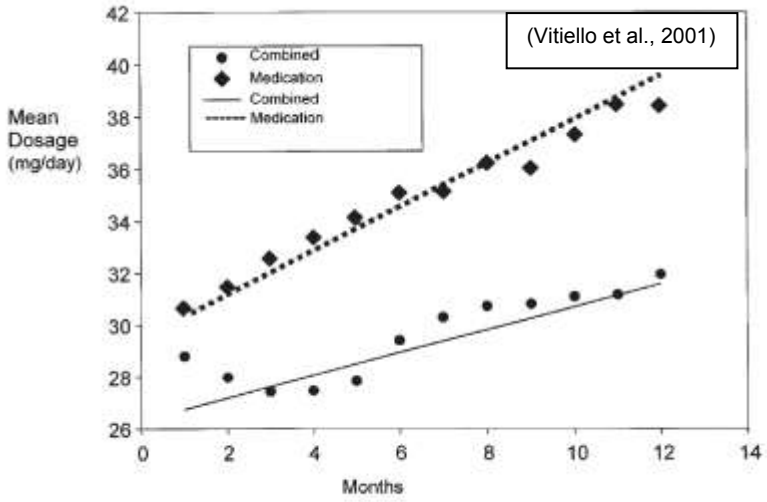

Fig. 2 Mean daily dose of methylphenidate during treatment maintenance by treatment group (combined treatment versus medication management).

These findings are not unique to the MTA. Numerous other extended follow-up studies of stimulant medication in children have observed a similar need to increase dose over time. In most studies with a long-term follow-up component, a 25% increase over the first year of treatment is typically seen. For example, the PATS protocol included a one year maintenance phase using the MTA algorithm to make changes in dose of medication over time. In this study, the average dose increased from 14 to 21 mg/day during this maintenance despite a month long double-blinded titration phase prior to the maintenance period. The same phenomenon has been observed in extension studies of once a day stimulants. For example, in the two year extension study of OROS-MPH (Concerta®), dose increased by 26% (on the average from 35 to 42 mg/day) even though subjects had been previously titrated to optimal dose (Wilens et al., 2005). These data do not include the additional 9% of subjects who dropped out specifically due to loss of effect even on the maximum dose of OROS-MPH. The mg/kg dose increased by 13 to 15%, suggesting dose adjustments were not primarily due to increasing body mass. The vast majority of this increase occurred in the first year of treatment even though efficacy assessments occurred only every 3 months. The fact that dose changed little in the second year was likely due to the high attrition rate in year two (nearly half the sample stopped prematurely) and that many subjects were at the maximum dose allowed in the study. Hence, the leveling off of dose was likely due to methodological factors rather than to the lack of tolerance to OROS-MPH. Similar results were found in extension study for AMP (Adderall XR®) (McGough, et al., 2005). After a weekly titration to define optimal dose, the mean dose was 16 mg/day. It increased by over a third to 20.2 mg at 6 months. Little incremental change was seen over the next year and a half.

Another possible mechanism driving the need to increase dose could be that parents adapt their expectations to their child's recent functioning. As stimulants typically do not resolve all ADHD symptoms (Jensen et al., 2007; MTA, 1999), parents may rate persistent, residual symptoms more severely as time passes. The increase in parent reported severity would then translate into increased dose. If parental adaptation of ratings was the primary source of the dose increase, then placebo replacement of medication should lead to immediate worsening of parental report. However, Martins found that placebo substitution on weekends did not lead to acute worsening in parent ratings of weekend behavior or teacher ratings of behavior during the subsequent week (2004). Likewise, Sleator found that the majority of youth on a stable stimulant

regimen for a year or more did not experience an acute worsening in symptoms ratings with transition to placebo (1974). However, no prior work has examined the impact of interrupted dosing on long term efficacy.

In summation, the literature reviewed above suggests that an appreciable dose increase is often needed for ADHD children to maintain full effect over the first year of treatment with stimulants. Dose increases are needed even when the dose has been systematically titrated, suggesting it is not due to initial under-dosing. Observed dose increases are greater than predicted by change in body weight alone, so it appears that children are not simply outgrowing their dose. This pattern occurs across stimulant classes and formulations, suggesting that tolerance may occur with any stimulant medication. Dose increases are an effective strategy to overcome this loss, at least in the first one or two years of treatment. However, if the need for dose escalation remained constant, untenable doses of stimulants might be required within a few years and dose escalations may not be a viable long-term strategy for the majority of ADHD youth prescribed CNS stimulants. In the MTA, only a third of the participants receiving medication demonstrated ongoing treatment benefit after two years, leading the authors to question the advisability of continuing medication in the majority of participants (Swanson et al., 2007). Long term outcomes were no better for medication adherent youth (Molina et al., 2009). Most longitudinal assessments have reached similarly disappointing conclusions about the observed long term benefits of stimulant medications (Hazell, et al. 2011). While alternate mechanisms may be responsible for the inability to detect long term benefits of stimulant medications, based on the collected evidence summarize above, it appears unwise to rule out tolerance to the therapeutic effects of stimulants as a contributing factor.

It is clear that the field needs to identify additional ways to sustain the initial, large clinical effects of stimulant medication. Fortunately, efficacious treatments for the management of tolerance have been developed for other diseases. Therefore, it seems prudent to prioritize assessing the role of tolerance in the long term management of ADHD over other possible mechanism for which we have no current treatments. One possible treatment is the use of prescribed drug holidays. They have been found to be efficacious for recovering lost effect in trials of anticonvulsants and opioid analgesics (Azar et al., 2010; Ho, Gan & Habib, 2006; White 2005). School day dosing was once the standard practice with many parents still preferring to dose primarily on school days (Pliszka 2007; Sleator, Newman & Sprrague, 1974). Drug holidays have even been prescribed as a means of preventing stimulant induced growth suppression (Faraone 2008). Evidence based behavioral treatment options exist (Fabiano et al., 2009; Pelham & Fabiano, 2008) that can be employed on days off medication to provide symptom relief. As reported above, Safer and Allen (1998) found that the vast majority of youth achieving a 50% symptom response were able to sustain this effect for 3 years or more. Interestingly, 85% of their sample used medication only on school days. Martins found that over 4 weeks, substitution of placebo for IR MPH on weekends produced little reduction in symptom control on weekends (2004). Hence, the increased morbidity from drug holidays for ADHD medication is likely less impairing than that for opioid analgesics where drug holidays are recommended to enhance therapeutic response (Dupen, Shen & Esrek 2007; White 2005). These results suggest that prescribed drug holidays are feasible and merit exploration as a means of combating tolerance.

An extended, controlled clinical trial that evaluates children in their naturalistic settings, similar to the MTA, would be the preferred design for examining the efficacy of prescribed drug holidays to reduce the need for recurrent dose increases and to improve long term symptom control. However, they are not ideal for the precise determination of pharmacodynamic response that may be necessary to identify drug tolerance. In these trials, dose adjustments can be caused by many factors that may have little to do with drug efficacy, such as parental preference or treatment adherence. Moreover, the commonly employed outcome measures of parent and teacher ratings are prone to rater expectancy bias (Waschbusch, Pelham, & Waxmonsky, 2009) that may further reduce the ability to identify changes in therapeutic efficacy. Analog classroom designs employing objective outcome measures are the preferred modality for detecting changes in efficacy at specific time points or for detecting subtle differences between agents with established efficacy (e.g., Pelham et al., 1999 for comparisons of Adderall and Ritalin). This paradigm (see Swanson et al., 2002) has been employed to aid the development of several stimulant formulations (e.g., Metadate CD: Swanson et al., 2004), and the concept of tachyphylaxis was first identified in the analog classroom setting. The most commonly used measure to detect incremental changes in efficacy is the 10 minute timed math test (MMT—dozens of studies—see below) where subjects are scored on the number of problems completed as well as the percentage completed correctly. Studies of extended release stimulants in analog classroom settings done by this investigative team have already suggested the capacity of CNS stimulants to impact next day behavior

even after they have cleared the body, presumably through producing an adaptation in the CNS (see prelim studies).

Preliminary Studies: Analog classroom measures have been widely used to evaluate the efficacy and time course of CNS stimulants (McCracken et al., 2003; Swanson et al., 1999/2005). The sensitivity of these lab school protocols have made it possible to document statistically significant differences related to subtle differences in dose and time of evaluation of medication. Even though neither was designed to assess tolerance, two such studies mention an unexpected finding suggesting carry-over tolerance.

Results from these published studies can be used to obtain an estimate of an effect size for long-term tolerance. In these designs, each medication condition is typically started 6 days before the analog classroom day, which consisted of 8 tests spread out across the day at 1.5 hour intervals. Hence, by the time subjects arrive in the analog classroom they have already been treated with a fixed dose of medication for almost a week. By comparing the performance on the initial test after 6 days of placebo to 6 days of active drug, we can estimate the carry-over tolerance from the prior exposure. For example, Swanson et al (2005) noted large positive effects on attention and behavior for Concerta® and Metadate CD® on the 10 minute math test (10-MMT) administered in the analog classroom 1.5 and 3.0 hours after dosing. However, on the preceding test administered immediately after the morning dose (before expected onset of effect), the effect sizes were moderately negative (for Concerta®, -0.33 for 18 mg, -0.25 for 36 mg, and -0.43 for 54 mg). The authors interpreted the temporary superiority of the placebo over the medication conditions results as possible evidence of tolerance. McCracken, Biederman, Greenhill, Swanson et al. (2003) also reported this initial temporary superiority of the placebo condition in a study of Adderall® and Adderall XR® but effect sizes were not reported. We will provide an effect size analysis of the Adderall® 10 mg and the Adderall XR® 10 mg (equivalent to Adderall 5 mg BID) conditions to show the magnitude of this effect the 10-MMT measure of performance (number of problems worked correctly). After the 6-day placebo exposure, performance was associated with better performance (86.7 problems) than after 6 days of drug exposure conditions (e.g., 56.2 problems for the 10 mg Adderall and 60.9 problems for 10 mg Adderall XR). The differences divided by the SD of the placebo condition (56.1) provides an estimate of effect size: (56.20 – 86.77)/56.1 = - 0.545 for Adderall and (60.95 – 86.77)/56.1 = -0.46 for Adderall XR. The test 1.5 hours later provides some indication of how this carry-over tolerance effect is overcome by the dose of medication on day 7. Based on these preliminary analyses of performance in lab school studies, we provide evidence that the build-up of tolerance over a 1-week period, has an effect size of about 0.4 for the 10-MMT measure for a standard dose of stimulant medication.

These results document that repeated exposure to CNS stimulants impacts objectively measured performance the day after the therapeutic effects of the medication have stopped, presumably through producing an adaptation in the CNS. This effect can be detected within the first week of medication use in analog settings. If declining performance on the MMT (administered when medication is active in contrast to the above studies) within a given subject tested repeatedly across days on a fixed, therapeutic dose of a CNS stimulant can be demonstrated, then tolerance to CNS stimulants has been demonstrated according to current definitions of the concept (Dupen, Shen & Esrek 2007). No prior study has attempted to do this task. These results also support that tolerance may occur within one week of dosing and that analog classrooms can measure performance with the necessary precision to detect tolerance.

Innovation

Numerous studies have documented the impressive capacity of CNS stimulants to reduce symptoms of ADHD over the course of weeks to months. In contrast, the MTA (Molina et al., 2009) and most other longitudinal studies (Barberesi et al., 2007, Marcus & Durkin 2011, Scheffler, et al., 2009) have failed to find that these short term benefits translate to appreciable long term advantages, even for those adherent to the medication. This great divide between the acute vs. chronic effects of treatment is one of the most vexing clinical dilemmas in the field today- How can a treatment that works so well at one time point not translate to sustained improvements over time? However, the phenomenon of diminishing effects over time is not unique to the treatment of ADHD. Multiple classes of medications exhibit reduced efficacy over time when used daily for extended durations, such as opioid analgesics (DuPen, Shren & Esrek 2007) and the anticonvulsants (Azar et al., 2010). This is in essence the definition of tolerance. For opioids, the concept of tolerance (i.e., repeated exposure decreasing the drug's effects over time) is well established as the need to increase dose to maintain effect is widely observed (Mao, 2002). Yet, despite similar observations for ADHD, tolerance to stimulant medications is thought by some leading researchers to not occur (Safer & Allen 1988; Vitiello et al., 2001). However, as we discussed above, the MTA and most other extended trials of CNS stimulants clearly document

a need to increase dose by 25% or more over the first year of treatment to maintain therapeutic effect (Greenhill et al., 2007; McCracken et al., 2003; Vitiello et al., 2001; Wilens et al., 2005). These dose increases surpass what would be expected by growth alone. Imaging data support the occurrence of changes in receptor density with repeated use of CNS stimulants (Volkow et al., 2012), which has been proposed as a possible neurobiological mechanism for the development of tolerance (DuPen, Shen & Esrek, 2007). Moreover, short term tolerance, or tachyphylaxis, has been established to occur within the day for CNS stimulants (Swanson et al., 1999). This discovery led to the development of truly effective extended release stimulants that have been one of the greatest revolutions in ADHD pharmacology over the last two decades (Pliszka, 2007; ACNP, 2011). These combined observations suggest that tolerance merits exploration as the mechanism underlying the disconnect between short and long term efficacy for CNS stimulants. If tolerance is identified with routine use of these agents for treatment of ADHD, then manipulations such as drug holidays that have successfully minimized tolerance for other CNS agents could prove efficacious for enhancing long term outcomes in ADHD.

There have been no controlled studies designed specifically to ascertain the occurrence of tolerance. Existing studies of stimulants and ADHD are comprised of large scale clinical outcome studies that measure effect primarily from monthly parent and teacher ratings in natural settings (MTA, 1999; Vitiello et al., 2001). These designs are ideal for documenting and comparing the efficacy and feasibility of prescribed treatments. However, limitations of symptom ratings of ADHD as well as the occurrence of multiple confounders that arise in extended clinical trials (nonadherence, missing ratings, selective dropout, parental treatment preferences, etc.) make it extremely difficult to determine if tolerance is the primary causal mechanism for the observed pattern of dose increases seen over time in clinical trials in natural settings with CNS stimulants. Moreover, only a subset of youth with ADHD require chronically escalating doses to maintain effect, suggesting that a within-subject design may be more appropriate to detect tolerance rather than large-scale, between-group studies where effects in a subset of participants could be missed. Therefore, we propose to use the same methods used to discover tachyphylaxis (within-day tolerance) in a within-subject design under tightly controlled conditions to ascertain if tolerance occurs across dosing days. Specifically, we will employ the 10 minute math test (10-MMT) in the analog classroom setting using a within-subjects, crossover design to compare drug response after 3 weeks of continuous OROS MPH treatment vs. 3 weeks of placebo with drug/placebo probes after each 3-week block. In addition, we propose to test under randomized conditions in the regular school year and home settings, whether 5-day-a-week (prescribed weekend drug holidays) dosing reduce the need for subsequent dose increases while sustaining initial medication effects compared to 7-day-a week (continuous) dosing. This study will be the first trial to examine if dosing schedule impacts total the need for dose adjustments, total daily dosage, and the level of symptom control.

Consistent with the NIH's desire to promote translational research, we have elected to unite the laboratory assessment of tolerance with the randomized clinical trial of weekly drug holidays vs. continuous dosing. The detection of tolerance in analog settings is of limited import if it does not alter outcomes in real world settings. By testing every subject on multiple days of OROS-MPH and placebo treatment and by including a drug-placebo probe following 3 weeks of OROS or placebo, we can create individualized tolerance indices in a controlled setting as well as as predictors of the need for dose adjustments in the natural setting. This will allow us to determine if subjects who manifest a diminishing response across days in the analog classroom are more likely to display worsening ADHD symptoms over the course of the school year despite being medicated and subsequently need to have their previously optimized dose further increased. This method maximizes precision by using the same subjects in both phases and cost-effectiveness by sharing staff, resources and recruitment efforts. *Most importantly, it allows us to correlate the need for dose changes in real world settings with the occurrence of tolerance in the laboratory, thereby linking the mechanism (tolerance) and outcome (dose increase) of interest. The observed association between these two stages is critical to the identification of tolerance as a causal factor for the need for dose increases so commonly observed in research and clinical work with ADHD children. If our translational study of the concept of tolerance is successful and our proposed intervention—weekend drug holidays—are effective, then a dramatic change many once again occur in long-term treatment of a disease impacting millions of children.*

In summary, the proposed research is of high import and innovation because it addresses one of the most recognized and treated psychiatric disorders of childhood (ADHD). It uses the established principles and techniques of pharmacology to identify a possible mechanism (long-term tolerance) for one of the most significant unanswered questions in the field to date, the unexplained loss of efficacy with long-term use of stimulant medication. Our work is both novel and innovative as it proposes to evaluate one potential solution to this dilemma while challenging the prevailing belief, in the absence of data, that long-term tolerance does not

occur. The same approach has been used to identify the occurrence of acute tolerance, which led to the development of the new generation of long-acting stimulants and a dramatic shift in prescribing practices. This application is derived directly from those experiences and integrates the experience, skills and knowledge of experts on the neuroscience of CNS stimulants and clinical outcomes in ADHD.

Approach

Participants*. Two-hundred and fifty children with ADHD between the ages of 6-12 will be recruited in 4 cohorts (N =63 per cohort) during Y01 to 04 of the project.* Recruitment will occur between January and June of each year. Each year, the cohort of participants will be recruited from among those families seeking to enroll their child in the Summer Treatment Program (STP) for Children with ADHD at Florida International University. The STP is an intensive 8 week summer camp for children with ADHD that was the model for the summer program employed in the MTA (MTA, 1999) and has received national recognition as a model clinical treatment program. All study participants will also be enrolled in the Summer Treatment Program (STP), as this is the setting for the analog classroom component of the study.

Based on prior experience, the participants are expected to be approximately 25% female and 75% male as these gender rates are representative of epidemiological prevalence estimates of ADHD in children (American Psychiatric Association, 2000; Visser et al, 2010). The combined population of Broward and Miami Dade Counties is approximately 57% Hispanic, 25% Caucasian, and 18% African American. Based on the local demographics and our previous trials in South Florida, We expect at least 50% minority enrollees (see targeted enrollment chart), surpassing the percentage in the MTA (MTA, 1999).

Recruitment*.* Participants will be recruited from applicants for the STP. In 2012, the STP enrolled 240 ADHD children and at least that number is expected annually. Our center has an extensive history of running large-scale, ADHD clinical trials, several of which have been set at the STP. Over the past 10 years, we have recruited more than 1000 ADHD children for a variety of federally-funded projects and STPs, including more than 500 since the CCF relocated to FIU in 2010.

Inclusion/Exclusion. Inclusion criteria will include a DSM-IV-TR diagnosis of ADHD, and a Full Scale IQ above 80. Exclusion criteria will include: currently or in the past 6 months receiving psychotropic medication for conditions other than ADHD or active medical or psychiatric conditions that could be worsened by stimulants (seizures, pregnancy, arrhythmias, hypertension, Tourette's Disorder, psychoses, mania etc*.,). Youth who meet full DSM IV criteria for Autism or Asperger's Disorder will be excluded as stimulants have been found to have reduced efficacy and tolerability in this population (Rupp Treatment Team, 2005).* Youth with a documented intolerance to methylphenidate medications or a failed trial of OROS MPH at full therapeutic doses will not be enrolled. Youth with comorbid ODD, CD or a mood or anxiety disorder not requiring psychotropic medication will be allowed to enroll as long as they do not need emergent treatment (mania, active suicidal ideation) as their conditions did not predict stimulant dose during the 13 months of randomized treatment in the MTA (Vitiello et al., 2001). Participants will be permitted to engage in community based psychosocial treatments but cannot start new psychotropic medication. The type and intensity of community based treatments with be measured using the Services for Children and Adolescents-Parent Interview that was used in the MTA (Jensen et al., 2004), and analyzed as a covariate.

Initial Assessment, Diagnosis, and Measures*.* At an intake assessment, informed parental consent and youth assent will be obtained. During this assessment**,** diagnosis of ADHD will be assessed through a combination of parent structured interview (NIMH Diagnostic Interview Schedule for Children IV, computerized version: Shaffer et al., 2000) and parent and teacher rating scales, as is the standard and recommended practice in the field including for adolescents (Pelham, Fabiano & Massetti, 2005; Wolraich et al., 2005). A dual clinician review procedure will be used to determine diagnostic status and where disagreement occurs, a third clinician will be consulted. Additionally, a clinician will administer to the child a brief intelligence test (WASI-II; Wechsler, 2011) and achievement testing (WIAT-III; Wechsler, 2011). Teacher ratings (Disruptive Behavior Disorders Rating Scale, Pelham et al., 1992; Impairment Rating Scale (IRS), Fabiano et al., 2006; *Academic Performance Rating Scale (APRS); DuPaul et al., 1991*) will also be obtained. As part of the Pittsburgh Modified Conners Rating Scale, *Parents and teachers will rate children's peer relationships from the SNAP rating scale on the (Atkins et al., 1985; Pelham et al., 2001). The APRS and peer relationship itsms will be repeated at study endpoint as measures of functional social and academic outcomes. Similarly, the Disruptive Behavior Disorders Rating Scale (Pelham et al., 1992) will be completed at baseline and endpoint by parents and teachers, as it rates all DSM IV symptoms of ODD, CD and ADHD. These measureshave been employed in multiple pharmacological trials for pediatric ADHD (Waxmonsky et al., 2010). The Coddington Life Events List (Coddington,1972) will also be administered at baseline to assess the degree of familial stressors. Life*

stressors will be analyzed as a covariate. The CBCL (parent version) will be used to assess for psychiatric comorbidity (Achenbach, 2009). If any subject scores in the borderline or clinical ranges on the anxious/depressed, withdrawn/depressed, social problem or thought problems subscales, parents will then complete all modules of the C-DISC. It has been used in numerous clinical trials as well as in epidemiological studies of pediatric mental illness (Costello, Egger & Angold, 2005). All DISC diagnoses will be reviewed by a MD/PhD level clinician prior to a formal decision on subject eligibility. Study physicians will also gather medical history and collect vital signs (resting pulse and BP, weight, height) to ensure it is medically appropriate for subjects to be prescribed stimulants. Study physicians will conduct their own exam or consult with the primary care provider if review of the medical history indicates the possibility of additional risk.

Phase 1: To assess for the development of tolerance to the therapeutic effects of stimulant medication in a controlled summer program setting.

The Lab School Protocol uses highly controlled settings and a surrogate measure of efficacy -- the 10-Minute Math Test (10-MMT) -- to gain precision. We will use these procedures for the evaluation of long-term tolerance during an 8-week Summer Treatment Program (STP. As an operational definition, we consider long-term tolerance to be reduced response to medication a day or more after prior exposure to medication. In contrast, we consider short-term tolerance (tachyphylaxis) to be the effects manifested to a given dose before the medication has cleared the body. In the 8-week STP, we can establish the classic conditions to test for tolerance by varying long-term exposure (e.g., two weeks or more) to stimulant medication that precedes a standard test on the optimal dose. Medication will be provided weekly to parents in the form of blister packs with each dose marked with day of the week it is to be given. Upon arrival to the STP, camp staff will verify that the participant took the scheduled dose of medication for that day. As part of the daily STP schedule, there are classroom periods in the midmorning (no earlier than 9:45 AM) and midafternoon (no later than 2:45 PM). The 10- MMT will be administered as part of each classroom period to provide a daily measure of academic productivity (averaged across the two classroom periods per day) that can be used as a measure of pharmacodynamic response to medication.

As part of the assessment for entering the STP, the baseline 10-MMT will be administered, which consists of 6 separate pages of math problems, each with a different level of difficulty (i.e., 1-digit addition, 1 digit addition or subtraction, 2-digit addition, 2-digit addition and subtraction, 3-digit addition, 3-digit addition and subtraction). This will be repeated twice, and on the second test the difficulty level that most closely approximates the target productivity rate of 10 problems per minute will be selected as the difficulty level for that child for all future tests. In this way, the difficulty level will be individualized and then held constant across the 8 week STP. Similar procedures have been used in summer programs and lab schools to precisely assess therapeutic effects of stimulant preparations (e.g., Pelham et al., 1987; 1990, 1999a,b, 2001; Swanson et al., 1998, 1999, 2002, 2003, 2005). We will use OROS®MPH, which achieves a constant effect from 1.5 to 10+ hours after administration (Pelham et al., 2001; Swanson et al, 2001; Swanson et al, 2003).

During the first two weeks of the STP, placebo-controlled assessments of up to four different OROS methylphenidate doses (18mg, 27mg, 36mg, 54mg,--max dose not to exceed 2mg/kg/day) will be conducted to establish each child's optimal dose. These doses cover the entire range of commercially available FDA approved doses for children ages 6-12. Study investigators will review teachers and counselor measures of efficacy (frequency counts of problem behaviors, percentage of academic seatwork assignments completed correctly, ratings of behavior during the camp day) and parent and counselor ratings of tolerability to establish each child's individual optimal dose (Pelham et al, 1985; Pelham & Hoza, 1987; Pelham et al, 1987, 1990, 1999a,b, 2005). Tolerability will be assessed using the Pittsburgh Side Effect Rating Scale (Pelham, 1993). Similar scales were used by the MTA during the month long medication titration phase (Greenhill et al 2001) and have been used in dozens of medication studies in the STP (see references above). Medication will not be administered on weekends during the titration period to give parents experience at applying learned behavioral treatments (that are part of the STP) when children are unmedicated, as they need to be prepared for weekend drug holidays that may be prescribed in the longitudinal follow-up phase.

Over the next 6 weeks, exposure differences will be established by a cross-over of 3-week treatments with optimal dose vs. placebo. Twice-daily assessments will be performed with the 10-MMT administered in each classroom period to establish a sensitive and reliable surrogate measure of efficacy as the 10-MMT has been the primary objective measure of treatment response used in analog classroom studies (Swanson, 2002). Before each condition, a 2-day (Saturday and Sunday) placebo washout will be imposed. During each exposure conditions, children will receive the same condition on weekends to extend the continuous exposure

period to 19 days for each condition. At the end (day 18 or 19) of each 3-week condition, a probe will be administered to create a drug-placebo contrast. Order of placebo or drug will be counterbalanced across participants on these two days. For the Placebo Exposure, the optimal dose will be inserted under double-blind conditions on day 18 or day 19, and for the Drug Exposure condition, a placebo will be inserted. This is shown schematically in Table 1. These probes will provide a drug-placebo difference balanced for other effects that may occur over time in the STP. Order of drug and placebo will be counterbalanced across participants such that half receive active medication first and half receive placebo first.

Behavioral interventions will not be employed in the classroom context when the MMT assessments are being gathered so as not to confound the behavioral and pharmacological effects and perhaps minimize the effect of medication. We have used this approach in multiple prior STP studies and have shown that it eliminates the potential confound (e.g., Carlson et al, 1992; Pelham et al, 1985,1993).

	Week/day	Monday	Tuesday	Wednesday	Thursday	Friday
Titration	1	Placebo	18 mg	27 mg	36 mg	54 mg
Titration	2	18 mg	27 mg	36 mg	54 mg	Placebo
Condition 1*	3	Med -1	Med -2	Med-3	Med-4	Med-5
Condition 1	4	Med-8	Med-9	Med-10	Med-11	Med-12
Condition 1	5	Med-15	Med-16	Med -17	Med or Pla-18	Med or Pla-19
Condition 2	6	Pla-1	Pla -2	Pla-3	Pla-4	Pla-5
Condition 2	7	Pla-8	Pla-9	Pla-10	Pla-11	Pla-12
Condition 2	8	Pla-15	Pla-16	Pla-17	Pla or Med-18	Pla or Med-19

*One group order is shown; drug and placebo will be administered in reverse order for half of the participants. Within each condition, there are two orders for drug vs. placebo testing with each subject getting the opposite assigned treatment on days 18 or 19 ensuring 17-18 days of constant exposure.

Dependent measures. The six weeks of the RCT phase will provide comparisons for proof-of-concept tests of the hypothesis of long-term tolerance. The efficacy measure (academic productivity on the 10-MMT) will be obtained twice a day for 15 STP school days. The drug-placebo difference for each of the 13 matched weekdays prior to the probe days will provide within-subject estimates of effect size with different histories of exposure for the preceding days. Based on experience, the initial effect size (estimated from the drug-placebo contrast on day 1 and 2) is expected to be large (e.g., ES ~ 1.0). If long-term tolerance emerges, the effect size derived from the individual drug-placebo differences should decrease over the 3 weeks; individual slopes will be calculated to determine these differences and analyzed as described below for study Aim 1. Since we have multiple tests administered each day, we will be able to obtain precise and stable measures of performance on the 10-MMT and an effect size for each individual. The placebo/drug probe at the end of each 3-week exposure will provide a second index of possible tolerance such that the effect size following 3 weeks of medication exposure is expected to be smaller than the effect size following placebo exposure. This second index of tolerance will be used to examine the relationship between the controlled measure of tolerance in the summer and the need for dose escalation during the following school year (Phase 2) in Specific Aim 2.

Phase 2: random assignment to continuous dosing regimen or weekend holidays for the school year. Monitor medication effectiveness and standardized need for dose escalation with monthly clinical visits modeled after the MTA protocol in which full effectiveness waned and was maintained by increases in dose.

At the end of the STP, participants will be randomly assigned to either 7 day-a-week (continuous) or 5-day-a-week (weekend drug holidays) dosing for the duration of the academic year (50% chance for each) to evaluate the impact of drug holidays on dosage requirements. Children will stay in their assigned groups (5 vs.7 day a week dosing during extended school breaks such as winter and spring break. Children will begin the school year on their established, optimal dose of OROS from Phase 1 of the study. Two prior placebo-controlled trials have found that a dose of stimulant in the STP/analogue classroom settings was comparably effective during the child's regular school setting (Pelham et al., 2001, 2002), so the transition from STP to school does not necessitate dose adjustments.

Procedures modeled after the MTA medication maintenance phase will be followed to collect monthly assessments of medication effectiveness and to determine the need for dose escalation (Vitiello et al., 2001). Initial treatment will remain stable for the first 4 weeks of the school year to allow for adjustment to the school setting and for the teacher to become familiar with the child. After 4 weeks, parents and children will attend monthly medication visits, where physicians will measure heart rate and blood pressure and will conduct a review of monthly ratings from teachers and parents. Prior to these visits, teachers and parents will complete

ratings of medication effects. Parent and teacher ratings of symptoms and impairment (see measures below) will be evaluated by the investigators to determine need for medication dose escalation. In both arms, children whose teachers or parents indicate continued efficacy of medication will remain on their current dose. If it is documented by the parent or teacher and affirmed by the physician investigators (see algorithm below) that symptoms have worsened, OROS MPH will be increased to next available dose (e.g. if at 36mg increase to 54mg) for participants in either arm. Functioning will be monitored for the following month, and the assessment will be repeated for the next visit.

Dose can be increased up to FDA-recommended daily maximum dose for the age, unless there are safety concerns or emergent adverse effects. Dosages may be lowered at any time. If a participant is still impaired on the maximum FDA dose, than they can be switched to amphetamine based medication such as mixed amphetamine salts XR. Switching stimulant classes is the recommended treatment when an initial stimulant trial is not successful (Pliszka, 2007). The timing of and the rationale for the switch will be documented. A switch in medication class was uncommon in the MTA (12%), *but nonetheless the percentage of subjects reaching maximum approved OROS dose and then percentage crossing over to alternate medication will be evaluated as a exploratory outcome if the N is sufficient (MTA, 1999).*

Measures and adjustment algorithm*. IOWA Conners and the Impairment Rating Scale are employed because they are brief and therefore more likely to be completed by teachers without complaint than more lengthy measures. They have been found to as reliable for detecting treatment change as longer scales (Pelham, Fabiano & Massetti, 2005). We have employed these measures and this approach to detecting need for dose escalation in the MTA and several previous NIH-and IES-funded studies (NIMH: MH0629046; IES: R324B060045). The IRS evaluates the child's functioning in developmentally important area of peer relationships, adult-child relationships, academic performance and classroom behavior. For this study, raters will be instructed on the IRS to rate the past month and compare it to the month prior in order to aide detection of tolerance. The IOWA Conners assesses the spectrum of ADHD and ODD symptoms. Both measures have been found to be a sensitive marker of medication effects (Fabiano, et al., 2006; Goyette et al., 1978). Parents will be specifically instructed to rate only school days when all subjects are medicated, so that symptom exacerbations on weekends in the drug holiday arm will not trigger a dose increase.*

The study physicians will review all of the collected ratings to evaluate each child's functioning and response to the current dose of medication. As classroom performance and behavior will be used to determine optimal dose in the STP, teacher ratings will be the primary determinant of dose. If ratings indicate that children's response is worse than the previous month, study staff members will contact the rater to rule out factors other than reduced response to medication (e.g., learning problems, external family stressors). If reduced responsiveness is determined, a dose increase will be recommended. Similar assessment measures and titration thresholds in multiple medication studies (Vitiello et al., 2001, Pelham et al., in preparation). Parents in both arms will also rate symptom levels specifically on weekends for the weekend before the visit to assess symptom levels during possible times off medication. A similar assessment protocol has been successfully employed in a current study by Dr. Waxmonsky assessing the effects of stimulants on growth (MH083692). Parents will also complete the Pittsburgh Side Effect Rating Scale (PSERS) monthly to evaluate adverse events.

Weekend medication will be blinded and dispensed in separate blister packs from the unblinded weekday medication to ensure that parents and prescribing physician are blind to treatment assignment. Families will be given only enough medication for the month and will be asked to track medication administration on a daily basis using dosing calendars to maximize adherence. Pill counts and dosing calendars will be reviewed at each visit to verify adherence to prescribed medication and drug holidays. To assess accuracy of parent report of medication adherence, a MPH saliva assay will be collected at 3 random medication visits during the course of the school year. Identical collection policies to that employed in the MTA will be used. The assays are sufficiently sensitive that administration of medication the prior morning will not produce a positive result the next day, even after repeated dosing (Modi et al., 2000; Papadopoulos, et al., 2009).

The ideal duration for a therapeutic stimulant holiday is unknown. Weekend holidays were selected because preliminary data suggests that tolerance can onset within days, so the offset may be as rapid. In support of this theory, anticonvulsant holidays as short as two days have been associated with improved seizure control (Azar et al., 2010). Further, weekend holidays are practical and commonly used in clinical practice to address side effect concerns (Pliszka, 2007) and been found to be well tolerated by families whose children are already stabilized on a daily medication routine (Martins, et al., 2004).

As part of their participation in the Summer Treatment Program, all parents will complete a behavioral parent training course (BPT; 8 group sessions) to give them the skills necessary to manage ADHD symptoms at home and to learn how to establish a school-based daily report card (DRC). *Monthly group "booster" BPT sessions addressing these topics will be held for the remainder of the school year in an effort to maximize retention. Similar "low dose" behavioral supports services have been provided to families in several of our recent longitudinal treatment studies (e.g., MH062946; IES R324B060045). They have proven helpful in increasing retention (mean annual attrition under 5% across three trials totaling 450 children). Provision of ongoing behavioral services is particularly relevant for this proposal as racial and ethnic minority families are more likely to benefit from and to adhere to combined treatment services for ADHD than medication alone (Arnold et al, 2003; Stein et al., 2012). Notably, less than a third of parents access these optional booster services with the mean number of sessions attended being less than 1 per year. Hence, it is unlikely that this level of behavioral support for parents will influence need for dose escalation based on teacher reports. As participants in both arms will have equal access to BPT, the comparison of the two dosing schedules should not be impacted. Behavioral interventions will not be implemented in the children's regular school settings by study staff so as not to influence need for dose increases (cf. the MTA, Vitiello et al., 2001). Instead, study staff will be available during the monthly booster sessions to assist parents in establishing a school-based daily report card. Teacher-implemented, usual-care classroom interventions will be tracked for analysis as a covariate.* ADHD medication will be provided through the study to minimize financial burden to families and to maximize treatment adherence.

Dependent Measures. *The number of dose changes needed per the protocol during the school year will be the primary outcome measure. Additional, secondary dosing outcomes will include time to first dose increase, mean endpoint total daily dose, and percent reaching maximum OROS dose. The index of tolerance manifested in the controlled STP setting (as described above) will be investigated as a predictor of putative tolerance (dose escalations) during the school year. In addition, at the end of the school year, the SSRS, APRS, LES, and DBD Rating will be repeated to measure endpoint symptoms (both ADHD and ODD), social skills, academic performance, and familial life events (secondary outcomes or covariates for analyses).*

Analytic Plan.

Aim 1: The critical test of tolerance in the STP will be based on the comparison of the final estimates of effect size based on the within-subject probes on Days 18 and 19 of each condition (see Table above). These tests will provide within-subject estimates of effect size for the same conditions (i.e., the optimal dose of OROS MPH), but with different histories of exposure for the preceding 3 weeks (i.e., either to medication or to placebo). Our operational definition of tolerance will be a smaller Drug/Placebo effect size after the Drug exposure than after the Placebo exposure. This planned t-test will be from the full ANOVA (see below). We propose additional planned tests (see below) embedded in an ANOVA that includes other factors to control for one between-subject factors (Order, with 2 levels: Drug/Placebo or Placebo/Drug) and one within-subject factor (Day, with 13 levels for the 13 weekdays in each condition prior to the placebo probe). This will provide a test of Drug/Placebo differences controlled for exposure on a day-by-day basis. Each difference will also represent an effect size, but the conditions will be offset by 3-weeks in contrast to the main planned comparison based on the drug-placebo probes at the end of each Exposure condition (see above). Using a mixed model ANOVA (SAS Proc Mixed), we will test for a differential change in performance (absolute score on the 10-MMT) for the Exposure conditions (Drug and Placebo). With a sample size of 200, the power to detect a difference with effect size of .4 is greater than 0.8, so power is clearly adequate with a sample of 250.

One planned test of tolerance will be based on a comparison of the average change in effect size for the 2 exposure conditions. Based on prior studies (see Preliminary Studies section), we expect that the tolerance effect in the STP setting will reach an effect size of about 0.4 after a week or more or exposure to stimulant medication. For a sample size of n = 200, and the average effect size of 0.4 for the group, the power to detect a difference in the two exposure conditions (Drug, Placebo) will be greater than 0.8.

Since we expect individual differences in tolerance, we will perform a test of the presence or absence of tolerance. We estimate the proportion of cases manifesting a smaller effect size after the Drug Exposure than after the Placebo Exposure condition. For a sample size of n = 200, and for an expected proportion who will show tolerance of 0.6, the power to detect a difference in direction of change will be greater than 0.8. The primary index of tolerance (drug/placebo differences on final days of exposure) will be used to address Aim 3.

Aims 2 and 3: The basic design is a two-arm randomized, double-blind, controlled clinical trial, with participating children being allocated 1:1 at the beginning of the school term to either a seven-day continuous dosing drug regimen or a five-day weekend-drug-holiday regimen. The allocation will be done with a permuted

block randomization strategy with block sizes 2 and 4. The participants will be followed for the full school term. The primary outcome will be the number of dose changes required during the entire school year for which will compare the two treatment arms using a Poisson regression model (secondary dose-related measures are described below). Number of dose changes was selected as the primary outcome as it is the direct measure of tolerance in this protocol. Symptom severity and social/academic impairment will be evaluated descriptively as secondary outcomes. All children are expected to show large improvement on these measures since all will be medicated at a therapeutic dose level and actively medicated at endpoint and we do not necessarily expect group differences on these variables. If our intervention is successful, outcomes may be similar although the doses for the weekend holiday group may be lower than the continuous dosing group.

We will also investigate the impact of the individual index of tolerance (**Aim 3**) and other covariates of interest (DBD scale ODD/CD symptom severity, gender and stressful familial life events) on the number of dose changes by including these terms in the regression model. This will permit useful estimates and tests of the impact of these factors on number of dose changes.

The expected number of dose changes for 7-days medication group is 2.76, based on the 13 month RCT phase of the MTA (Vitiello, et al., 2001). A sample size of n=250 (125 per treatment arm) should provide 95% power to detect at a least 25% decrease in the number of dose changes for the weekend drug holiday group, two sided test, $\alpha = 0.05$ (**Aim 2**). The power for assessing the impact of the individual index of tolerance (**Aim 3**) on the number of dose changes is above 95%. We recognize that use of OROS vs. short acting MPH (as was done in the MTA) may impact the number of dose changes. However, for a sample size 250, power remains above .8 to detect a 25% difference between groups if the average number of dose increases is as low as 1.6 in the 7 day a week dosing group. The maximum number of dose increases is four in this study due to limits on the maximum prescribed dose of OROS-MPH, which could decrease the power somewhat should this occur with sufficient frequency. However, our sample size of 250 should still provide adequate power. Also, should this occur with sufficient frequency, we can compare the proportions of the children in the two treatment arms for which dosage reaches the maximum threshold as well as the percentage crossing over to an alternate medication, which was 12 % in the MTA (MTA, 1999). We have run numerous longitudinal treatment studies including ones that similarly assigned subjects to specified treatment arms for a year's duration. In a current medication study set in South Florida (MH083693), we have experienced only a 5% attrition rate after one year. After adjustment for a 12% drug switch and 5% attrition rate--sample size drops to 208—power is sufficient to detect a 25% difference in the number of doses switches between group if the 7-day-a-week group averages 1.9 medication switches per year, a third less than what was observed in the MTA (Vitiello et al., 2001). We have multiple safeguards in place to maximize adherence as a threat to internal validity but results will also be analyzed by reported medication usage as well as by assigned treatment group.

The secondary outcome will be the time-to-change from the initial dose during the school year. We will compare the hazard rates for the two treatment arms with a Cox proportional hazard survival regression model. We can also investigate the impact of the individual index of tolerance and other covariates on the hazard rate ratio by including these terms in the regression model. In the MTA maintenance trial, 54% of the medication only group had their dose increased at least once during the 13-month maintenance phase. Therefore, the expected hazard rate for 7-days medication group will be 54% during the school year. A sample size of n=250 (125 per treatment arm) should provide about 80% power to detect a hazard rate ratio of about 1.69 (54% for 7 days medication from MTA/32% for weekend drug holiday), two sided test at $\alpha = 0.05$. The power for the test of the impact of individual index of tolerance (**Aim 3**) on the hazard rate ratio is considerably above 80%. Another potential outcome of interest is the time to the second dose change. The analysis will be very similar to that for the time to first change, but will have less power since the frequency of events will be lower. The difference of average final dose between two treatment arms will be compared by using two sample t-tests. Based on the results from Vitiello et al (2001), the expected final dose for weekend drug holiday (31.1+/-11.7 mg/day) will be lower than 7-days medication (38.1+/- 14.2 mg/day). A sample size 250 (125 per group) will provide 99% power to detect a difference at least 7mg/day using a two-sided two-sample t-test at significance level of 0.05. Furthermore, we will also investigate the impact of covariates on the average final dose by using a mixed model to take into account the possible dependent ratings from the same rater.

Protection of Human Subjects

1) Risks to the Subjects

a) Human Subjects Involvement and Characteristics

We will recruit 250 physically healthy children, ages 6-12 with ADHD who have no documented adverse response to stimulants. All human subjects' research will occur at the Center for Children and Families (CCF), an established multidisciplinary site for clinical trials of pediatric psychopathology led by Dr. Pelham. All investigators are faculty at the CCF, and Drs. Swanson, Waxmonsky, and Pelham are all well-experienced in conduct of NIH- and industry-sponsored clinical trials with stimulants (more than 50 studies among them). All assessments, medication visits and therapy sessions will occur at the CCF, the sole clinical site for this study.

b) Sources of Research Material

Information gathered during the study will be used for research purposes only and includes: (1) parent, clinician and teacher ratings of subject's ADHD symptoms and impairment (e.g., social, academic) at home and at school; (2) analog-classroom records of timed-math problems completed correctly; (3) semi-structured interview data; (3) physical health histories of the child; (5) saliva assay samples from subjects; and (6) records of medication administration. Only the clinical staff performing the assessments, medication visits and therapy sessions will have access to subjects' identities (approximately 10 staff). All information gathered is treated under the FIU Human Subjects Review Board guidelines for confidentiality of subject records. All data will be encoded and transmitted only in encoded form. Hard copies of data will be stored in a locked data storage room at the CCF. The sheet linking study code numbers to individuals will be stored in a separate locked filing cabinet.

c) Potential Study Risks and Protection against Risks

Risk: The primary risk to participants (children or parents) from the assessment sessions will be the time commitments and the stress of completing the necessary ratings and visits. Procedure: No invasive medical procedures (e.g., MPH sample collected via saliva sample, not blood test) will be performed during the study that would present any physical risk to the child subjects. The CCF has an established process for timely collection of these data that minimizes the burden on family and other raters (teachers). All raters will be trained using a manualized procedure for collection of data. The same treating clinician will meet with the subject and parents each time to minimize subject anxiety and provide continuity of care, similar to treatment at the subject's pediatrician.

Risk: Randomization to possibly undesirable treatment arm. Procedure: This minimal risk (neither treatment arm is undesirable, as both are standard stimulant treatment regiments) will be addressed through the informed consent/assent process, where parents and children will agree to be assigned to either group. Subjects will still have their dose optimized during summer analog classroom and all parents will be offered 8 sessions of group parent training during the summer and monthly group booster sessions during the school year to address symptoms accruing when medication is not active or not effective. In the revised treatment protocol, all subjects will be randomized to either 5 day a week (drug holidays) or 7 day a week dosing. Weekend medication will be administered in double blind fashion so participants will not know the difference between conditions. Dose increases will be standardized in both arms. Therefore, all subjects will be able to have their medication dose adjusted to address worsening symptoms. Finally, parents and children are free to withdraw from the study at any time and are not obligated to participate in a group they are assigned to. Withdrawing from this study will not affect any future interactions or their participation in any future clinical services or studies at the CCF.

Risk: Some children may experience symptom exacerbations during assigned weekend drug holidays. Procedure: Weekend drug holidays are a common clinical occurrence and have been found to be tolerable in research studies (Martins et al., 2004). In fact, a substantial number of ADHD children are treated clinically with medication on school days only, depending on physician and parent decision. Therefore, this risk would not be greater than that of routine clinical care. Medication will never be withdrawn on school days unless medically necessary. All families will participate in an 8 week course of parent training intervention to give them the basic therapeutic tools necessary to manage ADHD symptoms at home. Monthly behavior therapy booster sessions with experienced clinicians will also be available to families in both groups for the duration of the study so they will have access to professional guidance when they need it. In addition, all families are allowed to participate in community-based psychosocial treatments which should further decrease the risk of significant symptom exacerbations.

Risk: Financial costs of medication. Procedure: All subjects will be provided with medication free of cost for the duration of the study, providing a significant financial savings to families and assisting in recruitment efforts.

Subjects will not endure any costs from participation in the study other than the cost of transportation to the study site.
Risk: Blinding of weekend medication: This risk will be reviewed in the consent form. Parents will know that it is either their optimal dose or placebo. Study physicians will also be blinded. Unblinded medication will be used during weekdays (including any school days). The study pharmacist and data coordinator (who is available on weekends) will have access to blinding codes, so weekend medication status can be determined emergently if needed.
Risk: Side effects of stimulant therapy: irritability, appetite loss and insomnia are the most common adverse reactions to stimulant drug treatment. Other reactions that can occur in varying frequency include nausea, dizziness, stomachaches, headaches, tachycardia, skin rashes, drowsiness, motor movements (particularly of the mouth, jaw, and tongue) cognitive blunting, social withdrawal and other adverse emotional responses. Procedure: Many of these symptoms are transient and will disappear within a few days. The dosage range employed herein (.3-2mg/kg/day of MPH) is within the clinical standards. Because all of the participants in the proposed research will undergo structured medication assessments with gradually increasing dosages and because side effects often diminish with repeated exposures to stimulants, the likelihood of impairing side effects will be minimal. Side effects ratings will be collected for the duration of the study. In the event of side effects that need immediate attention, a study physician is on-call at all times. Dosage reduction often eliminates stimulant induced side effects and will be allowed during all phases of the study. In more severe cases, termination of treatment alleviates the symptoms. Standard procedures are used in case of any medical emergency. To ensure the safety of all subjects, Dr. Waxmonsky (a board certified child psychiatrist) or Dr. Humphery (child psychiatrist who speaks fluent Spanish) will be available by pager 24 hours a day during all phases of the trial. As part of the screening intake, all subjects will undergo a routine medical history by one of the study physicians to detect any health conditions that could be negatively affected by stimulants. If any abnormalities are detected, the child's pediatrician will be contacted to determine if stimulants would be medically advisable. Laboratory testing will be obtained if clinically indicated. Any child with health problems that could be predictably worsened by stimulant exposure will be excluded. As it is not standard practice to collect laboratory tests in healthy children taking stimulants, they will not be collected during the study unless clinically indicated.
Risk: Medical or professional intervention may be required in the event of side effects that need immediate attention. Procedure: A study physician is on-call at all times. Standard procedures approved by the governing IRB are used in case of any medical emergency.
Risk: There is some clinical evidence that stimulants lower the seizure threshold in children with a prior history of seizures or children with abnormal EEGs without seizure activity (Aldenkamp et al., 2006). Safe concomitant use of anticonvulsants and MPH has not been established. Procedure: Children with a history of seizure episodes requiring treatment (not including febrile seizures), or taking medication to control seizures will not be included in the study.
Risk: There are concerns about serious cardiovascular events in children treated with stimulants (Vetter, et al., 2008). Procedure: Children with hypertension, significant arrhythmias or other serious cardiovascular problems will not be enrolled in the study. A medical exam and physical exam will be performed by one of the study physicians prior to prescription of any medication. Based on the current AACAP and the American Academy of Pediatrics guidelines for stimulant usage, baseline EKGS will be performed only on subjects identified as having cardiac risk factors on the initial history and exam. The AHA recommendations regarding use of stimulant medication will be reviewed with all families and they will be offered EKG testing of their child. However, in accordance with AACAP's policy, only those children with identified risk factors will be required to undergo EKG testing prior to study entry. Results will be reviewed with the child's primary medical doctor before a decision on study enrollment is made. Risk factors would include pre-existing heart disease, symptoms suggesting significant cardiovascular disease, such as elevated blood pressure, or a family history of early onset cardiac events. Any child with documented, significant EKG abnormalities will be excluded. Blood pressure and pulse will be monitored regularly throughout the study. Resting blood pressure and pulse will be monitored at each visit to detect any clinically significant elevations in these parameters.
Risk: Parents may dislike some of the rating forms or answering some of the questions on the forms. Procedure: To address this risk, parents are not obligated to answer any question on the rating forms. They may skip any item they choose not to answer. Most parent rating forms are short, each taking less than 5 minutes to finish and none more than 20 minutes. For parents who wish, ratings will be read to them, and they will be permitted to answer orally. This will be offered as a standard option to all parents, so that any with

known or suspected reading difficulties will not feel stigmatized. All forms will be made available in English and Spanish so families may complete them in their primary language.

2) Recruitment and Informed Consent

Particiapnts will be drawn from the applicant pool for the STP. The STP serves an ethnically and racially diverse population including a large percentage of Hispanic patients. Because of the large Hispanic population in South Florida, measures will be taken to make the study accessible to parents and children who speak Spanish as their first language. A Spanish speaking physician is named on the grant and the center employs numerous research staff fluent in Spanish who can work on the grant. The consent form as well as assessment forms will be translated into Spanish.

Splitting the cohort into four 63-member samples, each recruited one year apart, should facilitate timely enrollment. We have budgeted a sizable amount for advertising, and the CCF has a marketing director who will oversee all recruitment efforts. The CCF is the only academic provider of evidence-based treatment protocols for pediatric ADHD in the Greater Miami region and operates a fully-functional outpatient pediatric mental health clinic on the FIU campus. This center specializes in the provision of evidence based treatments for disruptive behavior disorders. We have several ongoing initiatives with the Miami Dade School District (the fourth largest school district in the United States with over 350,000 students) which predominantly serves students of minority racial/ethnic status and has a school located on the FIU campus. In our 2 years in Miami, we have successfully recruited hundreds of ADHD youth for NIMH, IES and industry funded clinical trials and another 370 for summer treatment programs, demonstrating that we in fact can meet the goals for this study. For a current RO1(MH083692; PI Waxmonsky) examining the effects of stimulant medication on growth that is set here in South Florida, we have enrolled over 180 stimulant naïve children in 18 months for a medication treatment study. The majority of the sample is of Hispanic descent. Hence, we can successfully recruit large numbers of local ADHD youth including those of Hispanic ethnicity for medication trials. In this trial, we recruitment is divided into 4 annual cohorts so that no more than 63 subjects need to be recruited at any one time.

3) Potential Benefits of the Proposed Research to the Subjects and Others

The foremost benefit to subjects who participate in this project is that they will receive evaluation and treatment for their ADHD for one school year, by clinical staff experienced in the management of the disorder. Treatment will include regular monitoring of their performance at school and home. The school-year phase of the study was designed to mimic routine clinical treatment of ADHD, so both study arms are comprised of common clinical medication regimens for pediatric ADHD. The primary difference vs. clinical care is random assignment to 5 vs. 7 day a week dosing. Both of these dosing schedules are routinely employed in clinical practice so families will not be asked to endure any treatments that would not occur in routine clinical care. Any additional risks of study participation parallel those that would occur during routine clinical care (side effects of stimulants or the time burdens of behavioral therapy). The primary benefits vs. routine clinical care are treatment by expert clinicians in ADHD, frequent assessment and provision of all services at no cost. These direct clinical benefits in addition to the knowledge to be gained would seem to significantly outweigh the risks of the study.

4) Importance of the Knowledge to Be Gained

This research will enhance our understanding of the mechanisms of long-term tolerance to stimulant medication. It will also evaluate the relative efficacy of drug holidays and dose increases for correcting tolerance when it is demonstrated.

5) Data and Safety Monitoring

All data will be monitored for accuracy as they are collected by senior research staff, who will immediately contact raters who do not complete questionnaires thoroughly. Teacher ratings will be obtained via secure internet transmission, mail, or phone. Data obtained by phone interview will be recorded on paper forms. Medication administration records will be collected along with parent ratings to measure procedural integrity. Additional safety and efficacy data will also be collected at each visit. Research assistants will enter all of these data points on a rolling basis as the ratings are collected, and check these entries by comparing raw data ratings with computer printouts of the data sets, checking for and correcting any discrepancies. The data management process will be overseen by Elizabeth Gnagy who has served as our center's data coordinator for 20 years on 6 NIMH-funded clinical medication trials and multiple industry-funded trials. Ms. Gnagy will review all data collection procedures with study staff during weekly team meetings.

Study treatments are all derived from evidence based interventions and approved FDA dosing ranges for all medications will be employed along with systematic tolerability assessments. All clinician ratings will be completed by PhD/MD level clinicians experienced with pediatric ADHD. Medication adverse events will be recorded using the Pittsburgh Side Effect Rating Scale (PSERS) during each visit for the duration of the trial, and reviewed by Dr. Waxmonsky or Dr. Humphery. The PSERS was the primary side effect scale used in the MTA (MTA 1999; Pelham, 1993) and many other studies of stimulant effects. Safety measures to be performed at each assessment will include: weight, height, blood pressure and pulse. Additional examination of medical and mental health by study physicians will be performed as needed. Any time parents are concerned about possible side effects during the trial they may telephone the CCF or directly contact a study physician to speak with them about their concerns.

Any necessary medication adjustments including treatment discontinuation can be made during the assessment visits by the study physicians as our on-campus research pharmacy can process medication orders within 30 minutes. If a parent reports a tolerability concern between study visits, dose decreases to address adverse events may be performed at any time. All calls regarding tolerability concerns will be returned that same day as our center has physician on call 24 hours per day. The subject will be contacted (brought back to the CCF if necessary) to make any medication changes that may be needed. Any subject discontinuing study treatment due to tolerability concerns will be seen by a study physician to assess on treatment needs and referred to appropriate clinical programs within our center or in the community for ongoing care.

Dr. Waxmonsky will review all reports of potential serious adverse events (SAE) within 24 hours. If a serious adverse event does occur, the necessary reports will be filed with the governing IRB (Western IRB) by Dr. Waxmonsky and his staff within 24hrs. NIH will also be notified of any SAEs in the same timeframe. Regular notice of non-serious AEs will be provided on an annual basis to the NIH (yearly progress report), IRB (at each renewal) and DSMB (at every semi-annual meeting) unless requested more frequently. Issues regarding tolerability of study treatment will also be reviewed at weekly team meetings to ensure all staff are aware of current safety procedures and active cases with tolerability concerns.

This protocol is a large scale clinical trial of vulnerable subjects designed to assess loss of treatment efficacy over time and now includes some use of blinded medication. Therefore we elected to employ a Data Safety and Monitoring Board (DSMB) even though none is required, in order to ensure that study treatments (drug holidays) are not adversely impacting efficacy. The Data Safety Monitoring Board will consist of senior investigators in the etiology and pharmacological treatment of ADHD experienced in the conduct and analysis of large scale treatment studies. Dr. Wigal is Deputy Director of the Child Treatment Center at UC Irvine and has conducted numerous analog classrooms studies focusing on the efficacy of the stimulant medications. Dr. Arnold has published extensively on the tolerability and efficacy of ADHD medication over the past 40 years and currently supervises ADHD clinical services at Ohio State University. Dr. Wigal served as one of the MTA site investigators and Dr. Arnold was on the DSMB for the study. Both supervise large clinical treatment programs at their prospective sites. Dr. Nigg is a nationally researcher whose works focuses on the underlying mechanisms of ADHD as well as its associated neuropsychological impairments. The DSMB will meet via phone conference every 6 months to review findings and to determine if any adjustments need to be made to the provided treatments or other study methodology. At least one study PI will attend every meeting. Two weeks prior to meeting, the members will be provided with collected group level data on treatment efficacy, adherence and safety including detailed reports of each SAE that has occurred. If concerns arise about the results of a particular treatment group, then the DSMB may request that the study statistician (Dr. Williams) perform an interim statistical analysis. The DSMB will have the authority to modify study procedures or suspend enrollment if deemed necessary. The first meeting will occur prior to enrollment of any study subjects to ensure that all members deem study treatments safe and acceptable. Similar DSMB procedures are employed for another larger scale single site treatment study at our center FIU (MH086392).