UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA

CLAUDIA MACIEL SZOBOT

TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE E TRANSTORNO POR USO DE SUBSTÂNCIAS PSICOATIVAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O EFEITO CLÍNICO E CEREBRAL DO TRATAMENTO COM METILFENIDATO

PORTO ALEGRE, 2007

CLAUDIA MACIEL SZOBOT

TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE E TRANSTORNO POR USO DE SUBSTÂNCIAS PSICOATIVAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O EFEITO CLÍNICO E CEREBRAL DO TRATAMENTO COM METILFENIDATO

Tese apresentada como requisito parcial para a obtenção do título de Doutora em Psiquiatria, à Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Psiquiatria.

ORIENTADOR: FLÁVIO PECHANSKY

CO-ORIENTADOR: LUIS AUGUSTO PAIM ROHDE

PORTO ALEGRE, 2007

AGRADECIMENTOS

Ao Dr. Flávio Pechansky, orientador, pelo estímulo na construção de minha identidade profissional e pela ajuda em todas as etapas deste trabalho.

Ao Dr. Luis Augusto Rohde, co-orientador, pela incansável ajuda e pela generosidade em compartilhar seu vasto conhecimento. Também, a minha gratidão por ter estimulado e contribuído com uma linha de pesquisa em uso de substâncias psicoativas na adolescência.

Ao Dr. Rodrigo Bressan, do Laboratório Interdisciplinar de Neurociências Clínicas (LINC), Universidade Federal de São Paulo (UFSP), São Paulo, Brasil, pela inestimável colaboração no estudo de neuroimagem.

Ao Dr. Osvaldo Estrela, e colegas e funcionários da Irmandade Santa Casa de Misericórdia, Laboratório de Medicina Nuclear, pela fundamental colaboração ao estudo de neuroimagem.

Aos auxiliares de pesquisa Anelise Lusser, Betina Katz, Caroline Espanhol, Mariana Walcher, Pauline Ruaro, Paulo Eduardo B. Nunes e Thais Schaefer, pela extrema dedicação à coleta de dados.

Aos colegas e funcionários do Centro de Pesquisa em Álcool e Drogas do Hospital de Clínicas de Porto Alegre (CPAD).

Aos colegas do Programa de Déficit de Atenção do Hospital de Clínicas de Porto Alegre (PRODAH).

À secretária do PRODAH, Clarissa Paim, pela dedicação e eficiência em secretariar este projeto.

À coordenação dos Cursos de Medicina e de Psicologia da Universidade Luterana do Brasil, pelo incentivo e pela colaboração.

Á Indústria Farmacêutica Eli Lilly, pelo auxílio financeiro.

Ao Laboratório Toxilab, que gentilmente cedeu as análises urinárias para drogas de abuso para todo o projeto.

Aos Postos de Saúde do Município de Canoas.

Aos pacientes, e seus familiares, que aceitaram participar deste estudo e nos receberam em suas casas.

“It is a capital mistake to theorise before one has data.
Insensibly one begins to twist facts to suit theories
instead of theories to suit facts.”

Sherlock Holmes

Personagem criado por Arthur Conan Doyle (1859-1930),
médico e novelista inglês

RESUMO

A presente tese aborda a comorbidade entre o Transtorno de Déficit de Atenção/Hiperatividade (TDAH) e o Transtorno por Uso de Substâncias Psicoativas (TUSP) em adolescentes. Não há uma concordância na literatura quanto ao TDAH ser um fator de risco independente para o TUSP, ao considerar-se o efeito concomitante de potenciais confundidores. Esta é uma questão relevante, pois se de fato existir uma relação causal entre ambos os diagnósticos, como o TDAH inicia antes dos sete anos de idade e apresenta tratamentos efetivos, há um longo intervalo de tempo para o fortalecimento da prevenção primária ao TUSP. Independentemente de uma relação causal entre TDAH e TUSP, a presença de TDAH piora o prognóstico do TUSP. Até o momento, medicações de primeira linha para o TDAH, como o metilfenidato (MFD), não foram avaliadas em adolescentes com esta comorbidade. Além disso, é importante saber se a capacidade do MFD em bloquear o transportador de dopamina (DAT) é preservada mediante a presença do diagnóstico de TUSP, tendo em vista que as substâncias psicoativas (SPAs) ativam o sistema dopaminérgico. Neste trabalho, através de um estudo de caso-controle com adolescentes oriundos da comunidade, o TDAH esteve significativamente associado ao TUSP, mesmo ajustando-se os resultados para potenciais confundidores, como o Transtorno de Conduta (OR=9.12; $CI_{95\%}$ = 2.84-29.31 $p < 0.01$). Ainda, adolescentes com a comorbidade TDAH e TUSP participaram de um protocolo medicamentoso *crossover*, comparando o MFD-SODAS ao placebo, constatando-se um efeito significativo do tratamento com MFD-SODAS sobre os sintomas do TDAH ($p < 0.001$). Por fim, a ligação do MFD-SODAS ao DAT em adolescentes com TDAH e TUSP foi avaliada através de Tomografia Computadorizada por Emissão de Fótons (SPECT) com o

radiofármaco [^{99m}Tc]TRODAT-1 (radiofármaco com elevada afinidade pelo DAT). Após três semanas de uso de MFD-SODAS, houve uma redução significativa na disponibilidade do DAT em ambos caudato e putâmen, bilateralmente ($p < 0.001$ em todas as análises), concomitante a uma melhora clínica nos sintomas do TDAH, demonstrando que a medicação manteve o seu mecanismo de ação mesmo mediante o uso de SPAs. Concluindo, esta tese contribuiu com dados inéditos sobre a associação entre TDAH e TUSP no nosso contexto. Até onde saibamos, este foi o primeiro estudo a documentar o efeito do tratamento com MFD em adolescentes com TDAH e TUSP. Sobretudo, através do estudo de SPECT com [^{99m}Tc]TRODAT-1, pela primeira vez foi demonstrada a ação do MFD no DAT em sujeitos com TDAH e TUSP, o que é de suma importância para a base teórica dos protocolos clínicos de tratamento de TDAH em sujeitos com TUSP, área atualmente caracterizada pela escassez de estudos, sobretudo em adolescentes.

ABSTRACT

This study approaches the comorbitidy between Attention-Deficit/Hyperactivity Disorder (ADHD) and Substance Use Disorders (SUD) in adolescents. Up to now, there is no agreement in the literature whether ADHD would be an independent risk for the development of SUD, when results are adjusted to the presence of other covariates, such as Conduct Disorder (CD). This is a relevant issue, since ADHD has a very young age of onset and has effective treatments, allowing a long time interval for primary preventive interventions to SUD. Anyway, it is well established that the presence of ADHD is associated to a worst SUD prognosis in adolescents. However, first line medications for ADHD, such as methylphenidate (MPH), were not evaluated in adolescents with additional SUD. Moreover, it is important to know if MPH still blocks the dopamine transporter (DAT) in the presence of a SUD diagnosis, since most abused drugs also activates the dopaminergic system. In our study, through a case-control, community-based protocol, adolescents with ADHD presented a significantly higher odds ratio (OR) for illicit SUD than youths without ADHD even after adjusting for potential confounders, such as CD (OR=9.12; $CI_{95\%}$ = 2.84-29.31 $p < 0.01$). Adolescents with both ADHD and SUD underwent a 6-week, single-blind, placebo-controlled crossover study assessing efficacy of escalated doses of MPH-SODAS on ADHD symptoms. In this pharmacological trial, subjects had a significantly higher reduction in the Swanson, Nolan and Pelham Scale – version IV (SNAP-IV) and Clinical Global Impression (CGI) scores ($p<0.001$ for all analyses) during MPH-SODAS treatment when compared to placebo. At last, subjects underwent two single photon emission computed tomography (SPECT) scans with [Tc^{99m}]TRODAT-1, at baseline and after 3 weeks on MPH-SODAS, to assess MPH

binding at DAT. Clinical assessment for ADHD relied on SNAP-IV scale. After 3 weeks on MPH-SODAS, there was a significant reduction of SNAP-IV total scores ($p < 0.001$), and significant reductions of DAT Binding Potential at the left and right caudate. Similar decreases were found at the left and right putamen ($p<0.001$ for all analyses). In conclusion, this research line provided new data on the association of ADHD and SUD in our context. To the best of our knowledge, for the first time it was documented the effect of MPH on ADHD under current drug use, in adolescents. Also, we showed that MPH kept blocking DAT, similarly to what is found in ADHD patients without SUD comorbidity, providing neurobiological support for trials with stimulants in adolescents with ADHD+SUD.

LISTA DE FIGURAS

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

^{99m}Tc - Tecnécio^{99} metaestável

AACAP - American Association of Child and Adolescent Psychiatry

ADHD - Attention-Deficit/ Hyperactivity Disorder

AIC - Akaike's Information Criteria

ASSIST - Alcohol Smoking and Substance Screening Test

AUD - Alcohol Use Disorder

BD - Binding Potential

BeSUD - Before SUD (antes do diagnóstico de TUSP)

CB1 - Cnnabinoid Receptors type 1

CD - Conduct Disorder

CGAS - Clinical Global Impression Scale

CGI - Clinical Global Assessment Scale

CLR - Conditional Logistic Regression

CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico

DA - Dopamine

DAT - Transportador de dopamina

DAT1 - Gene do transportador de dopamina

DO - Dopamina

DRD4 - Gene do receptor D4 de dopamina

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, 4th edition

EC-DR - Enteric Coated Delayd Release

ECR - Ensaio Clínico Randomizado

EUA – Estados Unidos da América

ER – Efeito Reforçador

HCPA - Hospital de Clínicas de Porto Alegre

HR - Hazard Ratio

IC - Intervalo de confiança

IQ - Quocient of Inteligency

K-SADS-E - Schedule for Affective Disorders and Schizophrenia for Scholl-Age Children-Epidemiological Version

LF - Left Caudate

LP - Left Putamen

LT - Lifetime

MEM - Mixed Effect Model

MFD - Metilfenidato

MINI - Mini International Neuropsychiatry Interwiew

NI - Neuroimagem

OCC - Occipital cortex

ODD - Oppositional Defiant Disorder

OR - Odds Ratio

OROS - Osmotic Release Oral System

PI - Principal Investigator

PLA - Placebo

r – Correlation Coeficient

RAs - Research Assistants

RC - Right Caudate

RCT - Randomized Clinical Trial
RP - Right Putamen
RS - Reward System
SD - Standart Deviation
SERS - Barkley Side Effect Rating Scale
SES - Socioeconomic Status
SN - screening negative
SNAP-IV - Swanson, Nolan and Pelham Scale – version IV
SODAS - Spheroidal Oral Drug Absorption
SP - screening positive
SPAs - Substâncias Psicoativas
SPECT - Tomografia Computadorizada por Emissão de Fótons
SR - Sustained release
STR - Striatum
SUD - Substance Use Disorder
TC - Transtorno de Conduta
TDAH - Transtorno de Déficit de Atenção/Hiperatividade
TH - Transtorno do Humor
TN - Triagem Negativa
TOD - Transtorno de Oposição de Desafio
TUA - Transtorno por Uso de Álcool
TUSP - Transtorno por Uso de Substâncias Psicoativas
UFRGS - Universidade Federal do Rio Grande do Sul
UNESCO - Organização das Nações Unidas para Educação, Ciência e Tecnologia
US - United States
USA - United States of America
vROIS - volumetric Regions of Interest
WAIS - Wechler Adult Intelligence Scale
WHO - World Health Organization
WISC-III - Wechsler Intelligence Scale – 3ª edição

SUMÁRIO

1 INTRODUÇÃO

Existe uma forte associação entre o Transtorno de Déficit de Atenção/Hiperatividade (TDAH) e o Transtorno por Uso de Substâncias Psicoativas (TUSP), tanto em estudos clínicos quanto comunitários (KUPERMAN et al., 2001; MOLINA, PELHAM, 2003; ELKINS et al., 2007). Estima-se que 30% do pacientes com TUSP apresentam comorbidade com o TDAH (CARROL, ROUNSAVILLE, 1993; SCHUBINER et al., 2000), taxa significativamente maior do que a vista na população geral (POLANCZYK et al., 2007). Em função desta alta comorbidade, vários estudos vêm analisando o possível efeito do TDAH no risco de desenvolvimento de TUSP, ainda sem uma conclusão. Questiona-se, sobretudo, se o TDAH seria um fator de risco independente para o TUSP ou se tal associação seria, de fato, sustentada pelo Transtorno de Conduta (TC), altamente prevalente em indivíduos com TDAH (BIEDERMAN et al., 1997). Tal esclarecimento é de relevância na prevenção primária do TUSP, pois o TDAH inicia na infância, em geral antes do TC e da idade mais típica de experimentação de substâncias psicoativas (SPAs) (COSTELLO, EGGER, ANGOLD, 2006), proporcionando um tempo considerável para que medidas preventivas ao TUSP sejam instituídas.

Independentemente de o TDAH ser um fator de risco para o TUSP, é alta a co-ocorrência destes transtornos, e dados sugerem que o TDAH interfere negativamente no prognóstico do TUSP (ERCAN et al., 2003; WHITE et al., 2004). Assim, caracteriza-se a necessidade de um maior conhecimento do tratamento farmacológico do TDAH quando na vigência de TUSP, no sentido de favorecer um melhor prognóstico a estes pacientes. Até o momento, poucos estudos avaliaram o efeito clínico das medicações para o TDAH em

pacientes com esta comorbidade. Estudos específicos nesta população são necessários, visto que a maioria dos ensaios clínicos de tratamento farmacológico do TDAH exclui da amostra indivíduos com uso/abuso/dependência de álcool ou SPAs ilícitas. Como as SPAs interferem no equilíbrio dopaminérgico em nível *striatal* (KOOB, 2006; RODRIGUEZ DE FONSENCA et al., 2005; TZAVARA et al., 2006; VOLKOW, FOWLER, WANG, 2004) e como as principais medicações para o TDAH (psicoestimulantes, como o metilfenidato) são de ação prioritariamente dopaminérgica (SPENCER et al., 2006), talvez o efeito de fármacos como o metilfenidato (MFD), por exemplo, seja diferente na vigência de uso de SPAs. Até o momento, não há dados publicados sobre a efetividade do metilfenidato em adolescentes com TDAH e TUSP.

Estudos de neuroimagem (NI) têm sido fortes aliados na compreensão do mecanismo de ação do MFD, como os realizados através de Tomografia Computadorizada por Emissão de Fótons (SPECT) com o radiofármaco [^{99m}Tc]TRODAT-1. O TRODAT-1 é um derivado tropano que quando marcado com Tecnécio^{99} metaestável (^{99m}Tc) cruza a barreira hematoencefálica e, por possuir elevada afinidade pelo transportador de dopamina (DAT; mesmo sítio de ação do MFD), ao ser captado pela cintilografia em modo SPECT, produz uma imagem sítio-específica do DAT, *in vivo* (MEEGALLA et al., 1997). Estudos em indivíduos com TDAH tratados com MFD mostraram significativa redução na ligação do [^{99m}Tc]TRODAT-1 após o uso de medicação (DRESEL et al., 2000; KRAUSE et al., 2005; LA FOUGERE et al., 2006). Tais dados ainda não foram, no entanto, replicados em sujeitos com TDAH e TUSP. A melhor compreensão do funcionamento cerebral do MFD em sujeitos com TDAH e TUSP pode ser útil para a base teórica dos protocolos clínicos de tratamento desta prevalente comorbidade.

A presente tese avaliou a associação etiológica entre TDAH e TUSP em adolescentes masculinos oriundos da comunidade (Artigo 1). Também, analisou-se o efeito clínico e

cerebral, através de SPECT com [^{99m}Tc]TRODAT-1, do MFD em adolescentes com TDAH e TUSP (Artigos 2 e 3, respectivamente).

Inicialmente, faz-se uma breve revisão sobre a associação entre TDAH e TUSP, sobre o tratamento farmacológico de adolescentes com TDAH e TUSP e sobre NI em sujeitos com TDAH e TUSP. Posteriormente, são apresentados os três artigos principais da tese. Por fim, junto aos anexos, constam um artigo de revisão sobre TDAH/TUSP e um capítulo de livro sobre bases neurobiológicas de TUSP na adolescência.

2 REVISÃO DA LITERATURA

2.1 Comorbidade entre Transtorno de Déficit de Atenção/ Hiperatividade e Transtorno por Uso de Substâncias Psicoativas

O TDAH acomete de 3 a 7% das crianças em idade escolar (POLANCZYK et al., 2007) e 4,4% dos adultos (KESSLER et al., 2006). O diagnóstico, de acordo com o *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV), está baseado na tríade desatenção/ hiperatividade/ impulsividade, presente desde antes dos sete anos de idade e em um padrão inadequado para a etapa do desenvolvimento. Os sintomas devem ocorrer em ao menos dois ambientes distintos. O diagnóstico diferencial, como por exemplo com o Transtorno Afetivo Bipolar, é fundamental (AMERICAN PSYCHIATRIC ASSOCIATION, 1994). Os sintomas do TDAH tendem a permanecer ao longo da vida adulta em até 55% dos casos (MANNUZZA, KLEIN, MOULTON, 2003), com prejuízos em diferentes áreas do funcionamento do indivíduo. As crianças e adolescentes com esta síndrome apresentam um risco aumentado de desenvolver outras doenças psiquiátricas na infância, adolescência e idade adulta, como comportamento anti-social, transtornos de humor e de ansiedade (SPENCER, BIEDERMAN, MICK, 2007). Em um artigo de revisão, BARKLEY (2002) enumera uma série de prejuízos apresentados por pacientes com TDAH ao longo da vida: menor progressão acadêmica, maiores taxas de demissão, maiores taxas de infração de trânsito e acidentes automobilísticos, início de vida sexual mais precoce, maior número de parceiros sexuais e menor cuidado contraceptivo. Há uma série de estudos relatando a associação entre TDAH e TUSP, cogitando-se uma relação causal entre ambos.

Uma das hipóteses é de que parte do risco para o TUSP poderia ser explicada pela presença de TDAH, já que o TDAH inicia muito precocemente (antes dos sete anos), vários anos antes do primeiro contato do indivíduo com SPAs (em geral, na adolescência intermediária).

Há um corpo de estudos apontando que, aproximadamente, 75% dos pacientes usuários de SPAs apresentam comorbidades psiquiátricas, como o TC, o TDAH e os Transtornos do Humor (THs) (BUKSTEIN, GLANCY, KAMINER, 1992; CLARK et al., 1997). Os dados da literatura não são concordantes, no entanto, em relação ao TDAH ser um fator de risco para o TUSP em adolescentes isoladamente do TC, como será revisado a seguir. Em última análise, apesar da alta comorbidade entre TDAH/TUSP, o risco poderia ser, na verdade, carregado pelo TC, presente em grande parte dos sujeitos com TDAH (BIEDERMAN, 1991). Outras possibilidades, no entanto, também podem existir, como a de uma propensão genética em comum, ao menos parcialmente, para TDAH e TUSP. Neste sentido, o gene do transportador de dopamina (DAT1) já foi apontado como tendo efeito tanto no TDAH (TODD et al., 2005) quanto no TUSP (GUINDALINI et al., 2006), assim como o gene do receptor D4 de dopamina (DRD4) (TODD et al., 2005; SHAO et al., 2006).

A melhor forma de averiguar a natureza da associação entre o TDAH na infância e TUSP na adolescência seria através de estudos longitudinais comparados, ajustando os resultados para os diferentes confundidores. Entretanto, esta alternativa é pouco viável, seja pelos longos anos de seguimento que seriam necessários, seja pela impossibilidade ética de diagnosticar TDAH na infância e não instituir um tratamento. Desta forma, a relação causal entre TDAH e TUSP vem sendo estudada a partir de diferentes enfoques metodológicos, ainda sem um consenso. Em uma tentativa de organizar o grande volume de publicações que, direta ou indiretamente aborda este foco, a revisão a seguir é apresentada a partir do tipo de amostra estudada: adultos com TUSP, adolescentes com TUSP, adultos com TDAH e adolescentes com TDAH. Posteriormente, comentaremos de que forma o TDAH poderia

influenciar no risco para TUSP e qual o efeito do tratamento do TDAH desde a infância no risco de desenvolver TUSP.

Estudos sobre **adultos com TUSP** (em geral, usuários de cocaína) constataram uma prevalência de TDAH ao redor de 35%, o que é significativamente maior do que o esperado na população geral (CARROL, ROUNSAVILLE, 1993; SCHUBINER et al., 2000). Os estudos sobre **adolescentes com uso problemático de SPA** também apontam para uma maior taxa de TDAH, não ficando claro se a associação pode ser atribuída ao TDAH isoladamente ou se seria pelo TC comórbido. KUPERMAN et al., (2001) encontraram uma maior prevalência de TDAH entre adolescentes usuários de álcool, em comparação a controles. Neste estudo, 72,2% dos jovens dependentes de álcool apresentavam diagnóstico de TDAH, TC ou TDAH em comorbidade com TC. Em um estudo de caso-controle com adolescentes internados por alcoolismo, observou-se a prevalência de 25% de TDAH, sugerindo-se que tanto o início quanto o seguimento da dependência de álcool são influenciados pelo TDAH (ERCAN et al., 2003). Em outros estudos semelhantes, a prevalência de TDAH também se mostrou elevada (DEMILIO, 1989; HORNER, SCHEIBE, 1997). Apesar destes dados não auxiliarem muito no entendimento da possível participação do TDAH na gênese do TUSP, pelas características da amostra e pelo delineamento, eles reforçam a importância de revisar sistematicamente a presença do TDAH em amostras clínicas de indivíduos com TUSP.

Outra forma de analisar a associação entre TDAH e uso problemático de SPAs é através de estudos com **adultos com TDAH.** BIEDERMAN et al., (1995) encontraram, em sujeitos com TDAH, a prevalência de 52% de uso problemático de SPAs ao longo da vida, em comparação a 27% nos controles (dados ajustados para comorbidades psiquiátricas como personalidade anti-social). Outro estudo encontrou dados semelhantes, além de constatar que os sujeitos com TDAH apresentavam maior risco de recaídas em comparação aos controles sem TDAH (BIEDERMAN et al., 1998). O maior risco para o desenvolvimento de TUSP em

adultos com TDAH foi confirmado por outros estudos, embora nem sempre mediante o controle de confundidores (LAMBERT, HARTSOUGH, 1998; MURPHY, BARKLEY, BUSH, 2002). Observa-se que os estudos com este enfoque apontam uma maior prevalência de uso de SPAs nesta população e indicam um pior prognóstico para a dependência química.

A literatura apresenta uma série de estudos sobre **adolescentes com TDAH**, cujos resultados diferem bastante. No tratamento para uso de SPAs, os adolescentes com TDAH demonstraram mais prejuízos pelas SPAs e maior fissura (HORNER, SCHEIBE, 1997). Há trabalhos que não encontram associação entre TDAH e TUSP em adolescentes (BIEDERMAN et al., 1997; DISNEY et al., 1999; MANNUZZA et al., 1991; WEISS et al., 1985). A maioria destes estudos, entretanto, não controlou os resultados para o tratamento do TDAH, podendo-se argumentar que uma vez tratado o TDAH, o seu potencial risco para uso problemático de SPAs estaria sendo significativamente minimizado, como já sugerido por WILENS et al., (2003) e BARKLEY et al., (2003).

Há diversos relatos, em contrapartida, de uma associação positiva entre TDAH e TUSP, embora nem sempre ajustando os resultados para os efeitos do TC e/ou outros confundidores. MANNUZZA et al., (1993) detectaram que o abuso de SPAs foi significativamente mais prevalente em pacientes com TDAH (16%) em relação a controles (3%) [Odds ratio (OR) = 4,6], na idade média de 18 anos. Este mesmo grupo, em outro estudo com sujeitos com TDAH na idade média de 25 anos, relatou a prevalência de 12% de abuso de SPAs ilícitas nos casos, em comparação a 4% nos controles (OR = 3,8) (MANNUZZA et al., 1998). Através de um estudo de coorte controlado, que acompanhou adolescentes com TDAH dos 13 aos 18 anos, observou-se que os probandos apresentaram maiores taxas de uso de álcool e outras SPAs (MOLINA, PELHAM, 2003). TAPERT et al., (2002) acompanharam por oito anos 66 adolescentes oriundos da comunidade e sem o diagnóstico de TDAH (portanto, sem intervenção medicamentosa), mas com prejuízo atencional medido por testes

neuropsicológicos. Os resultados demonstraram que os adolescentes com habilidades atencionais limitadas estavam em maior risco para uso patológico de álcool e outras SPAs, e quanto piores os escores em atenção/execução no início do seguimento, maior o consumo de maconha.

As últimas publicações conservam a tendência de resultados discrepantes. Um estudo norte-americano acompanhou ao longo de dez anos 140 crianças e adolescentes com TDAH e 120 controles (retenção: 80% dos casos; 88% dos controles), onde no último ano 36% da amostra com TDAH recebeu algum tratamento. Os autores descreveram que o grupo com TDAH apresentou significativamente mais uso regular de nicotina, álcool ou SPAs ilícitas em comparação aos controles [Hazard ratio (HR) = 2,7, 2,3 e 2,2, respectivamente] (BIEDERMAN et al., 2006). Outro estudo norte-americano, prospectivo e com amostra comunitária, avaliou três grupos de adolescentes: TDAH sem comorbidades [tamanho amostral (n) = 27], TDAH + TC ou Transtorno de Oposição e Desafio (TOD) (TC ou TOD = Transtorno Externalizante; n = 82) e controles (n = 91), constatando que o TDAH aumentou o risco para TUSP apenas na presença de um Transtorno Externalizante (AUGUST, HOEWOOD, RIDDER, 2006). Neste mesmo sentido, um estudo longitudinal com adolescentes da Nova Zelândia detectou que dificuldades atencionais na infância só conferiam risco maior para TUSP na adolescência se tal processo fosse mediado por problemas na linha anti-social (FERGUSSON et al., 2007). Tornando a questão ainda mais interessante, outro estudo longitudinal norte-americano, com amostra comunitária, detectou que a presença do diagnóstico de TDAH estava associada ao maior risco para uso de nicotina (OR = 2,1) e SPAs ilícitas (OR = 2,82), mesmo ajustando os resultados para a presença de TC (ELKINS et al., 2007).

Ainda, um estudo comunitário avaliou o efeito do TDAH sobre a idade do primeiro consumo de bebida alcoólica e sobre o intervalo de tempo entre o primeiro consumo e a

dependência alcoólica. Apesar de o TC ter sido o mais forte preditor, a presença de TDAH esteve independentemente associada com menor idade de primeiro consumo [HR = 1,52, intervalo de confiança (IC) = 1,18 – 1,96] (SARTOR et al., 2007). Ainda em relação ao álcool, MOLINA et al., (2007) detectaram que, entre adolescentes e adultos jovens, a idade parece interferir, visto que nos jovens com idade entre 15 e 17 anos, o diagnóstico de TDAH esteve significativamente associado ao beber pesado e às intoxicações alcoólicas. Já nos adultos jovens (idade superior a 18 anos), o TDAH perdeu a influência, que passou a ser assumida por sintomas anti-sociais.

A Tabela 1 sumariza os principais estudos sobre a associação entre TDAH e TUSP.

Tabela 1 - Estudos sobre a associação entre TDAH e TUSP

Autor	Delineamento e Amostra	Principais Resultados
A) Amostra: indivíduos com TUSP		
Carrol and Rousanville, 1993	Prevalência; clínica; 298 adultos; usuários de cocaína.	TDAH em 35% da amostra.
Kupermann et al., 2001	Prevalência; comunitária; 54 adolescentes com TDAH.	Maior taxa de TDAH do que na população geral; Diagnóstico de TDAH precedeu TC, que precedeu TUA.
B) Amostra: adultos com TDAH		
Biederman et al., 1995	Longitudinal; comparado; clínica; 120 TDAH e 120 controles.	TDAH: maior risco para TUSP (52%) do que controles (27%).
Biederman et al., 1998	Caso-controle; clínica; 239 TDAH e 268 controles.	TDAH: maior risco para TUSP.
Murphy et al., 2002	Caso-controle; 96 TDAH (clínico) e 64 controles (comunidade).	TDAH: maior taxa de TUSP.
C) Amostra: adolescentes com TDAH		
Weiss et al., 1985	Longitudinal (15 anos); clínica; sem cegamento; 63 TDAH e um grupo controle.	Similar taxa de TUSP entre casos e controles.
Biederman et al., 1997	Longitudinal; clínica; 140 TDAH e 120 controles.	O risco para TUSP não variou de acordo com a presença de TDAH.
Molina and Pelham, 2003	Longitudinal; clínica; 142 TDAH e 100 controles.	A persistência de TDAH e TC estiveram, independentemente, associadas a maior uso de SPAs.
Biederman et al., 2006	Longitudinal (10 anos); clínica; 140 TDAH e 120 controles.	TDAH: maior taxa de uso regular de nicotina, álcool e SPAs ilícitas (HR= 2,7, 2,3 e 2,2, respectivamente).
August et al., 2006	Longitudinal; comunitária; 27 TDAH; 82 TDAH+TC ou TOD; 91 controles.	TDAH: mais associado ao TUSP apenas mediante a presença de TC e/ou TOD.
D) Amostra: adolescentes sem TDAH ou TUSP		
Disney et al., 1999	Prevalência; 626 pares de gêmeos com 17 anos; comunitário; ambos os gêneros.	TDAH: sem efeito no TUSP, após ajustar resultados para a presença de TC.
Tapert et al., 2002	Longitudinal (8 anos); comunitário; 66 jovens sem TDAH mas com prejuízo atencional.	Escores basais de atenção e execução tiveram poder preditivo positivo para abuso e dependência de maconha 8 anos mais tarde.
Gau et al., 2007	Longitudinal (3 anos); 428 escolares (dos 12 aos 15 anos).	TDAH esteve independentemente associado ao TUSP (HR = 3,5).
Fergusson et al., 2007	Longitudinal (25 anos); comunitário; coorte de 1.265 bebês nascidos na Nova Zelândia.	Associação entre problemas atencionais precoces e TUSP é mediada pelo TC.
Sarter et al., 2007	Prevalência; 1269 adultos jovens (20,1 anos); masculinos; comunitário.	TDAH independemente associado a menor idade de primeiro consumo de álcool (HR = 1,52, CI 1,18-1,96).

Nota: TDAH = Transtorno de Déficit de Atenção/Hiperatividade; TUSP = Transtorno por Uso de Substâncias Psicoativas; TUA: Transtorno por Uso de Álcool; SPA = substância psicoativa. OR = Odds Ratio; HR= Hazard Ratio; TC = Transtorno de Conduta; TOD = Transtorno de Oposição e Desafio.

Estudos indicam que o tratamento farmacológico do TDAH esteve associado com uma redução de 85% no risco de uso problemático de SPAs em comparação a pacientes com TDAH e sem tratamento (OR = 0,15; IC = 0,04 – 0,6) (BIEDERMAN et al., 1999). Em revisão da literatura sobe TDAH e MFD, WILENS et al., (2003) encontraram resultados sugestivos de que a farmacoterapia com estimulantes na infância está associada a um menor risco de problemas com álcool e outras SPAs na adolescência (OR = 5,8). BARKLEY et al., (2003), em um estudo longitudinal, também não detectaram uma associação causal entre o tratamento com psicoestimulante na infância e adolescência e maiores taxas de experimentação, uso, dependência ou abuso de SPAs no início da vida adulta. Esses são dados importantes, pois demonstraram que o psicoestimulante, quando utilizado para fins do tratamento do TDAH desde a infância, além de não induzir ao uso de SPAs, minimiza o risco do TUSP, indiretamente suportando os dados de uma associação causal entre TDAH e TUSP.

Apesar de não haver um consenso na literatura sobre qual a real influência do TDAH no TUSP, constata-se que um sólido corpo de estudos embasa a possibilidade de uma ligação independente entre tais condições. Considerando o aparecimento da psicopatologia a partir de uma perspectiva do desenvolvimento, crianças e adolescentes com TDAH acumulam prejuízos tipicamente referidos na literatura de TUSP como aumentando o risco para experimentação e uso regular de SPAs na adolescência, como baixa auto-estima e prejuízos acadêmicos (TARTER, 2002). Do ponto de vista neurobiológico, através de estudos de NI e neuropsicologia, TDAH e TUSP partilham alguns modelos de risco, como disfunção dopaminérgica, disfunção executiva e disfunção no sistema de recompensa (KALIVAS, VOLKOW, 2005; NIGG, CASEY, 2005; SEIDMAN, VALERA, MAKRIS, 2005; FISCHER et al., 2005; SONUGA-BARKE, 2002; VOLKOW, FOWLER, WANG, 2004). Também, TDAH e TUSP podem ter influências genéticas em comum, como por exemplo, a proporcionada pelo gene DAT1 (ARON, POLDRACK, 2005).

A elucidação da real associação entre TDAH e TUSP é de relevância clínica, como destacado, pois pode interferir em prevenção primária ao TUSP ao permitir a identificação precoce de crianças de risco. Também, caso o TDAH seja um fator de risco independente ao TUSP, seria importante a adaptação das campanhas de prevenção ao uso de SPAs ao modelo cognitivo dos sujeitos com TDAH. Como o debate na literatura internacional segue aberto, existe a clara necessidade de mais estudos no assunto, com uma metodologia que permita diferenciar os efeitos do TDAH e do TC sobre o TUSP. Da mesma forma, não há estudos nacionais sobre o tema. Como o uso de SPAs também é influenciado por características regionais, com diferenças registradas em diferentes regiões do Brasil, por exemplo (GALDUROZ et al., 2005), é importante conhecermos como é a associação entre TDAH e TUSP especificamente no nosso contexto. O fato de o presente estudo ser desenvolvido no Sul do Brasil é relevante, pois, de acordo com a Organização das Nações Unidas para Educação, Ciência e Tecnologia (UNESCO) (2002), Porto Alegre liderava, recentemente, o *ranking* dos usuários regulares de SPAs lícitas e ilícitas, com 14,4% de usuários de álcool, 4,7% de maconha, 1,4% de cocaína e 1,1% de inalantes.

2.2 Tratamento farmacológico do TDAH em comorbidade com o TUSP em adolescentes

Embora o tratamento do TDAH envolva uma abordagem múltipla, a psicofarmacoterapia tem papel fundamental no manejo dos sintomas centrais do transtorno. A literatura claramente apresenta os estimulantes como as medicações de primeira escolha para o TDAH (GREENHILL, 1999), existindo mais de 150 estudos controlados (destes, mais de 100 com amostras de crianças e adolescentes) demonstrando a sua efetividade a curto prazo no transtorno. Cerca de 70% dos pacientes têm respostas robustas aos psicoestimulantes e os

toleram bem (AMERICAN ACADEMY OF PEDIATRICS, 2001; SPENCER et al., 1996). Em alguns países, como nos Estados Unidos (EUA), o psicoestimulante mais prescrito é o MFD (ZARIN et al., 1998), sendo, também, o único disponível no Brasil. Os estudos sugerem que todos os estimulantes melhoram os sintomas básicos do transtorno igualmente (AMERICAN ACADEMY OF PEDIATRICS, 2001).

Acredita-se que o MFD exerça o seu efeito terapêutico no TDAH bloqueando o transportador de dopamina (DAT) localizado principalmente no *striatum*, assim aumentando a disponibilidade de dopamina na fenda sináptica (SCHWERI et al., 1985). Contudo, estudos também referem uma ação terapêutica dos psicoestimulantes sobre o comportamento hiperativo em ratos desprovidos de transportadores de dopamina (GAINETDINOV et al., 1999), indicando que estes fármacos também atuem em outros sistemas de neurotransmissão.

Diferentes estudos demonstram uma associação entre a gravidade dos sintomas do TDAH e a gravidade do uso de SPAs (TAPERT et al., 2002), e entre a presença de TDAH e um pior prognóstico da dependência química (ERCAN et al., 2003; WHITE et al., 2004). Assim, entende-se que o TDAH deva ser devidamente tratado, concomitante a intervenções específicas para o TUSP.

Apesar de mais de uma centena de estudos controlados ter avaliado os efeitos do MFD no TDAH, a vasta maioria desses estudos excluiu da sua amostra sujeitos com uso/abuso/dependência de álcool e/ou SPAs ilícitas. Considerando-se que tanto o MDF (SPENCER et al., 2006), quanto as principais SPAs (KOOB et al., 2006; RODRIGUEZ DE FONSENCA et al., 2005; TZAVARA et al., 2006; VOLKOW, FOWLER, WANG, 2004) afetam o sistema dopaminérgico, os efeitos clínicos do MFD documentados em sujeitos com TDAH sem TUSP não podem, necessariamente, ser generalizados para indivíduos com TUSP. A literatura refere pouquíssimos estudos sobre o tratamento farmacológico do TDAH em sujeitos com TUSP, sendo a sua maioria com adultos. Interessantemente, dados

neurobiológicos oriundos de modelo animal documentam diferenças no sistema dopaminérgico ao longo do desenvolvimento, questionando a replicabilidade dos resultados oriundos de adultos para populações mais jovens. BADANICH, ADLER, KIRSTEIN, 2006, em modelo animal, demonstraram que adolescentes e adultos diferem na disponibilidade de dopamina na fenda sináptca. Também, a liberação dopaminérgica seguida à administração de cocaína difere entre adolescentes e adultos, no sentido de resposta mais intensa nos indivíduos mais jovens (STANSFIELD, KIRSTEIN, 2005). Com base nestes dados, observa-se a importância de estudos sobre os efeitos terapêuticos do MFD em sujeitos que apresentem a comorbidade TDAH e TUSP. Tais estudos devem, preferencialmente, contemplar diferentes etapas do desenvolvimento cerebral.

Em adolescentes com TDAH e TUSP, o único estimulante avaliado foi o pemoline, demonstrando efeito sobre o TDAH, mas pouca ação no consumo de SPAs (RIGGS et al., 2004). Entretanto, o pemoline não é mais utilizado, em função da toxicidade hepática, de forma que o contexto atual é de inexistência de dados com os psicoestimulantes recomendados para o TDAH (metilfenidato e anfetaminas) (American Association of Child and Adolescent Psychiatry, AACAP, 2002). Além deste estudo, existem dois outros, ambos com bupropriona (que não é uma medicação de primeira linha no TDAH) (AACAP, 2002). RIGGS et al., (1998) através de um estudo aberto de cinco semanas, avaliaram a bupropiona em 13 adolescentes com TDAH e TC, internados por uso de SPAs. A autora relatou melhora nos sintomas do TDAH, e não houve aferição do efeito quanto ao uso de SPAs. SOLHKHAH et al., (2005) avaliaram o efeito da bupropiona *sustained-release* (SR) nos sintomas de TDAH em 14 adolescentes com TDAH, TUSP e transtorno do humor, através de um estudo aberto de seis meses. Houve uma redução significativa tanto nos sintomas do TDAH quanto no consumo de SPA. Não foram encontrados Ensaios Clínicos Randomizados (ECR) com a bupropiona em adolescentes com TDAH e TUSP.

Mesmo em adultos com TDAH e TUSP, existem poucos estudos sobre o efeito do MFD. LEVIN et al., (1998), em um estudo aberto de 12 semanas com 12 adultos com TDAH e TUSP (cocaína), avaliaram a ação do MFD SR, demonstrando efeito terapêutico sobre os sintomas de TDAH, redução na fissura e menor uso de cocaína. A autora sugere que a redução da impulsividade e a melhora na concentração, com o tratamento do TDAH, podem aumentar a eficácia de algumas abordagens para o uso de SPAs, como a prevenção de recaída, utilizada no seu protocolo. Apesar de outro estudo aberto com MFD em adultos com TDAH/TUSP (cocaína) haver reportado efetividade sobre os sintomas do TDAH e melhora no consumo de cocaína (SOMOZA et al., 2004), alguns estudos controlados não demonstraram superioridade do MFD em relação ao placebo (CARPENTIER et al., 2005), ou em relação ao placebo e bupropiona (LEVIN et al., 2006) nos sintomas do TDAH. SCHUBINER et al., (2002), através de um ECR comparando MFD com placebo em adultos usuários de cocaína, demonstrou redução significativa nos sintomas de TDAH (P = 0,0039) e uma redução na fissura por cocaína. Entretanto, este estudo teve aproximadamente 47% de perda amostral. Destaca-se que nenhum dos estudos referidos documentou problemas com uso indevido do MFD, ou piora no uso de SPAs. Por fim, não há relatos na literatura de ECR avaliando a efetividade do MFD em adolescentes com TDAH/TUSP. Outras medicações para o TDAH, como a atomoxetina, também não foram avaliadas (tanto em adultos quanto em adolescentes).

Um dos possíveis motivos para a escassez de estudos com o MFD em sujeitos com TDAH e TUSP seria a preocupação com o seu potencial de abuso, visto que já foi documentado o seu efeito reforçador (ER) em humanos (RUSH et al., 2001). Estudos a partir de adolescentes com uso problemático de SPA referem que os psicoestimulantes são abusados neste grupo. GORDON et al., (2004), encontraram a prevalência aproximada de 30% de uso abusivo de psicoestimulantes em adolescentes com TUSP (31% da amostra com TDAH).

WILLIAMS et al., (2004) a partir de 450 adolescentes usuários de SPA, encontraram a prevalência de 23% de uso indevido de psicoestimulantes. Em sujeitos sem o diagnóstico de TUSP, também parece haver uso indevido de psicoestimulantes. Há relatos, na mídia norte-americana, de adolescentes hígidos utilizarem o MFD para aumentar o seu desempenho acadêmico e físico, e para fins de euforia (AACAP, 2002). O uso de MFD foi avaliado em uma escola norte-americana, vendo-se que mais de 16% dos alunos utilizou-o de forma recreacional, por via oral, e 12,7% esfarelou-o para usar de forma aspirada (BABCOCK, BYRNE, 2000). Nos EUA, recentemente, viu-se que, entre 4.580 universitários, 6% referiram uso de psicoestimulante no último ano, e 8% positivaram para uso na vida (75% usavam anfetaminas e 25% MFD) (TETER et al., 2006).

É importante destacar que estudos indicam que quantidade expressiva dos sujeitos que faz uso indevido de estimulante não é paciente com TDAH. Existe uma preocupação na literatura de pacientes com TDAH repassarem a sua medicação para outros que irão abusá-la. Em uma amostra de adolescentes norte-americanos em uso de MFD por indicação médica, 16% referiram que outros estudantes lhes pediram MFD, ou pediram para comprá-lo ou para trocá-lo por outra mercadoria (MUSSER et al., 1998). Analisando-se o perfil do paciente abusador de MFD em um Centro de Toxicologia, viu-se que 85% dos casos de adolescentes intoxicados com MFD não eram de usuários regulares, ou seja, não era medicação prescrita a estes adolescentes, mas que possivelmente eles pediram ou negociaram o MFD com conhecidos seus que o recebem com fins terapêuticos (KLEIN-SCHWARTZ, MCGRATH, 2003). Considerando-se especificamente amostras de indivíduos com TDAH, há poucos dados a respeito do abuso de estimulantes. Em adolescentes e adultos jovens com TDAH, viu-se que 11% vendiam a medicação para terceiros, 22% abusavam da medicação prescrita e 10% referiam sensação de *high* (como euforia, decorrente do ER) na dose prescrita (WILENS et al., 2006). Neste sentido, observou-se que crianças e adolescentes com TDAH, mediante

doses terapêuticas de MFD, podem apresentar efeitos subjetivos associados aos ER do MFD (MARTIN et al., 2007). Tamanha é a preocupação com o uso indevido de estimulantes, que o assunto foi tema de um editorial no *Americal Journal of Psychiatry* por parte do *National Institute on Drug Abuse* (VOLKOW, 2006). O ER dos estimulantes é de importante consideração não apenas em usuários de SPAs, mas também para o tratamento de TDAH em sujeitos sem TUSP e população geral: quanto mais o MFD for utilizado de forma indevida, maiores, possivelmente, as barreiras para que essa medicação seja administrada a quem, de fato, a necessita. Interessantemente, os estudos nos últimos anos esclareceram que o potencial de abuso do MFD depende, em muito, de propriedades farmacocinéticas e da via de administração, que determinarão a velocidade e a intensidade de ocupação e desocupação do DAT. Conforme VOLKOW et al., (1995), na ausência de um aumento intenso e súbito de dopamina, e na ausência de um rápido decréscimo desta substância, menor a chance de ER. Como o MFD, clinicamente, é utilizado por via oral, tal administração proporciona um perfil de aumento de dopamina muito diferente do que o visto, por exemplo, com a cocaína via aspirada, ou com o próprio MFD aspirado ou injetado. Estudos de NI têm sugerido que novas formulações de MFD, que resultam em menor pico de dopamina, apresentam menor ER (SPENCER et al., 2006). No Brasil, atualmente, além do MFD de curta ação, estão disponíveis outras duas formulações de MFD, ambas de liberação prolongada: MFD *Osmotic Release Oral System* (MFD OROS) e MFD *Spheroidal Oral Drug Absorption* (MFD SODAS). Assim, especialmente em dependentes químicos com TDAH, as novas formulações de MFD seriam preferíveis, mas evidências científicas precisam confirmar essa hipótese.

Em suma, ainda não há algoritmos para o tratamento do TDAH quando em comorbidade com TUSP, caracterizando uma área com clara necessidade de mais estudos. Futuros estudos devem, preferentemente, utilizar formulações de MFD que proporcionem

menores picos de dopamina, o que poderia evitar o uso indevido de estimulantes neste grupo de pacientes, possivelmente mais vulnerável por já apresentar um diagnóstico de TUSP.

2.3 Neuroimagem no tratamento farmacológico com metilfenidato do TDAH em comorbidade com o TUSP.

Inicialmente, salienta-se que, no TDAH, os exames de NI devem ficar restritos a situações de pesquisa, não tendo, até o momento, qualquer função clínico-diagnóstica (AACAP, 1997). Entretanto, tais exames têm sido muito úteis para uma melhor compreensão da base nerobiológica do TDAH (para uma revisão, ver KRAIN, CASTELLANOS, 2006). Os estudos de NI também têm sido importantes para o melhor entendimento do mecanismo de ação do MFD. Um dos métodos de NI mais utilizado neste sentido é o SPECT com radiofármacos altamente específicos, como o ^{99m}Tc-TRODAT –1, específico para o DAT. Assim, um estudo de SPECT com este marcador permite avaliar o grau de ocupação do DAT. Quanto maior a ocupação dos sítios de DAT pelo radiofármaco [^{99m} Tc]TRODAT-1, menor a atividade dopaminérgica.

Alguns estudos avaliaram, através de SPECT com [^{99m} Tc]TRODAT-1, o efeito do tratamento com MFD em sujeitos com TDAH, encontrando, em unanimidade, uma redução na ligação do [^{99m} Tc]TRODAT-1 ao DAT mediante o uso de MFD (indicando que o DAT passou a ser ocupado pelo MFD, seu sítio de ação). DRESEL et al., (2000), por exemplo, avaliaram o efeito cerebral de 15mg/dia de MFD de curta ação em 17 adultos com TDAH, constadando-se que a ligação ao TRODAT passou de 1,43 para 1,00 ($P < 0.001$). Outros estudos acharam resultados similares (LA FOUGERE et al., 2006; KRAUSE et al., 2005).

Apesar de também haver um sólido corpo de estudos de NI em sujeitos com TUSP (para uma revisão, ver VOLKOW, FOWLER, WANG, 2004), até momento, não encontramos estudos de NI avaliando especificamente sujeitos com TDAH e TUSP. Da mesma forma, o efeito cerebral do MFD em sujeitos com esta comorbidade ainda não foi documentado. O SPECT com [^{99m} Tc]TRODAT-1 permite inferências sobre a ocupação do DAT pelo MFD, sendo então um método adequado a este propósito. O maior entendimento da base neurobiológica sobre o mecanismo de ação do MFD nesse grupo específico de sujeitos pode contribuir com a base teórica necessária para os estudos clínicos de tratamento do TDAH em comorbidade com TUSP, ainda tão escassos.

3 OBJETIVOS

A presente linha de pesquisa em Transtorno Déficit de Atenção/Hiperatividade e Transtorno por Uso de Substâncias Psicoativas tem três objetivos gerais (contemplados, respectivamente, através dos artigos 1, 2 e 3):

1º) Avaliar a associação entre TDAH e TUSP, em uma amostra de adolescentes oriundos da comunidade;

2º) Avaliar o efeito do MFD SODAS, em comparação ao placebo, nos sintomas do TDAH em adolescentes com TUSP;

3º) Avaliar o efeito do MFD SODAS no transportador de dopamina, através de SPECT com [^{99m} c]TRODAT-1, em adolescentes com TDAH e TUSP.

4 CONSIDERAÇÕES ÉTICAS

Todos os pacientes e responsáveis receberam os esclarecimentos necessários sobre o projeto e, concordando com a participação, foram integrados aos protocolos após a assinatura dos respectivos Termos de Consentimento Livre e Esclarecido, aprovados pelo Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre.

Os investigadores assumiram, com os pacientes do projeto, um compromisso de sigilo das informações. Entretanto, como o projeto também envolve menores de idade, foi exposto ao adolescente que diagnóstico de TUSP, e outras situações de risco porventura relatadas, não seriam omitidas dos pais ou responsáveis.

Encerrada a participação no estudo de caso-controle, oferecemos tratamento a quem apresentasse o diagnóstico de TDAH, independentemente da presença de TUSP. Pacientes com TDAH e TUSP que satisfizeram os critérios de inclusão e de exclusão para o estudo farmacológico, foram convidados a ingressar no mesmo. Os pacientes sem o diagnóstico de TDAH, mas com outro diagnóstico psiquiátrico, foram encaminhados à rede pública.

Pacientes do protocolo medicamentoso (*crossover*, três semanas em cada intervenção – placebo e MFD SODAS) receberam placebo por três semanas. Esta conduta não fere nenhum protocolo já em vigor para pacientes com TDAH e uso concomitante de SPAs, uma vez que é uma área ainda pouco estudada, predominando ainda abordagens mais embasadas em pontos de vista individuais (“como eu trato”) do que em fluxogramas de tratamento, pois os mesmos inexistem para esta situação clínica, sendo esta inclusive uma das justificativas para a execução do presente projeto. O protocolo medicamentoso apresenta riscos moderados, relacionados ao uso do MFD SODAS. Este fármaco, no entanto, já foi (e vem sendo) utilizado

em crianças, adolescentes e adultos em centros nacionais internacionais. Os adolescentes e seus pais foram devidamente orientados sobre o objetivo do estudo. Os investigadores médicos estiveram disponíveis para qualquer emergência através dos números de telefone particular e/ou do setor do hospital em que estavam alocados. Após o término do protocolo, os pacientes permaneceram conectados à equipe por mais um mês, ou mais, se necessário, e depois foram encaminhados à rede pública. Após o estudo, para aqueles pacientes que se beneficiaram do MFD SODAS e não tiveram condições de aquisição, foram, se o quiseram, medicados com o MFD de curta ação, financeiramente mais acessível. Se necessário, era encaminhado o formulário de requisição de medicamentos especiais para a Secretaria da Saúde do Estado do Rio Grande do Sul, programa que está em vigor no nosso meio.

O protocolo de NI consistiu em realização de exames com alta tradição em estudos sobre TDAH, assim como o [^{99m}Tc]TRODAT-1. Não há relato na literatura de nenhuma intercorrência seguida a SPECT com [^{99m}Tc]TRODAT-1.

O presente estudo, e seus respectivos adendos, foram submetidos e aprovados pela Comissão de Ética do Hospital de Clínicas de Porto Alegre (aprovada pela CONEP e como um IRB pelo *Office for Human Research Protections, United States of America* - IRB 00000921).

5 ESTUDO 1 - QUESTÃO DE PESQUISA

Existe uma associação independente entre TDAH e TUSP, em adolescentes masculinos oriundos da comunidade?

ARTIGO PRINCIPAL 1

Is Attention-Deficit/ Hyperactivity Disorder associated with illicit Substance Use Disorders in male adolescents? A community-based case-control study

***Addiction*, 2007; 102(7):1122-30**

Word count: 3780

Is Attention-Deficit/ Hyperactivity Disorder associated with illicit Substance Use Disorders in male adolescents? A community-based case-control study

Szobot, Claudia M M.D.; Rohde, Luis A M.D., Bukstein, Oscar M.D.; Molina, Brooke S.G Ph.D; Martins, Caroline; Ruaro, Pauline; Pechansky, Flávio M.D.

From the Center for Drug and Alcohol Research, Hospital de Clínicas de Porto Alegre (HCPA), Federal University of Rio Grande do Sul (UFRGS), Brazil: Szobot CM, Pechansky F. From the ADHD Outpatient Clinic, HCPA, UFRGS: Rohde LA. From the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, USA: Bukstein O, Molina SGB. From the Lutheran University of Brazil, School of Medicine: Szobot CM, Martins C, Ruaro P.

Address correspondence and reprints requests to Claudia M. Szobot, Centro de Pesquisas em Álcool e Drogas, Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos, 2350. CEP 90035-003. Porto Alegre, Brasil. e-mail: **cmszobot@terra.com.br**

This study was partially supported by research grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) (Grant 307780/2004-0), Hospital de Clínicas de Porto Alegre and an unrestricted Grant from Eli-Lilly.

ABSTRACT

Aims: This study aims at evaluating the association between Attention-Deficit/Hyperactivity Disorder (ADHD) and illicit Substance Use Disorders (SUD) (marijuana, cocaine, and inhalants), controlling for the association with Conduct Disorder (CD), in a community-based sample of adolescents. **Design:** Case-control, community-based study. **Setting:** A delimited geographical area in the South of Brazil, served by 4 public health clinics. **Participants:** 968 male adolescents (15 to 20 years of age) were screened for SUD in their households. Out of the subjects who were screened positive, we selected 61 cases with illicit SUD. For each case we selected, from the group which was screened negative, 3 controls without illicit or alcohol SUD, matched by age and proximity with the case's household. **Measurements:** The screening instrument was the Alcohol Smoking and Substance Screening Test (ASSIST). SUD diagnoses were assessed by the drug section of the Mini International Neuropsychiatry Interview (MINI)**.** Other psychiatric diagnoses were based on semi-structured (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version; MINI) and clinical interviews. **Findings:** Adolescents with ADHD presented a significantly higher odds ratio (OR) for illicit SUD than youths without ADHD even after adjusting for potential confounders (CD, ethnicity, religion, and estimated IQ) (OR=9.12; $CI_{95\%}$ = 2.84-29.31 $p < 0.01$). **Conclusions:** Our results suggest an association between ADHD and illicit SUD in Brazilian adolescents that is not mediated by CD. These findings are potentially important from a prevention perspective because treatments are available for ADHD.

Keywords: ADHD, marijuana, cocaine, inhalants, substance use disorders, adolescent, conduct disorder

INTRODUCTION

Adolescent substance use disorder is a major mental health concern (1, 2). Illicit drug abuse and dependence (SUD) is associated with multiple impairments, such as high rates of drug-related car accidents (3) and psychiatric disorders (4). Marijuana is the most abused illicit drug worldwide, with an annual prevalence of 2.5% and affecting mostly young populations (5).

Both childhood externalizing disorders and their underling neuropsychological dimensions have an important role in the pathways to adolescent SUD. Neurobehavioral disinhibition at 12-14 years of age predicts SUD at 19 years of age (6, 7). Although Conduct Disorder (CD) is clearly associated with a higher liability to adolescent SUD (8), much debate remains regarding the association between ADHD (a diagnostic manifestation of disinhibition) and illicit SUD. Four possible interactions may exist: a) ADHD might have an independent effect on adolescent SUD liability; b) A detectable effect of ADHD on adolescent SUD might be mediated by CD, since the comorbidity between ADHD and CD is extremely high in community and clinical samples (9, 10); c) ADHD can simply coexist with SUD, without a causal relation; or d) ADHD and SUD might share a common genetic vulnerability. The dopamine transporter gene (DAT1) and the dopamine receptor D4 gene (DRD4), for example, have been implicated in the etiology of both ADHD (11) and SUD (12, 13).

ADHD is overrepresented among adolescents in treatment for SUD (14) and SUD prevalence is higher in clinic samples of children with ADHD followed to late adolescence than in non-ADHD comparison youths (15, 16). In another clinic sample of children with ADHD, severity of inattention predicted multiple substance use outcomes (17). Additionally,

inattention at age 15 predicted SUD 8 years later in a community sample (18). Some studies, however, did not find an independent association between ADHD and adolescent SUD. Disney et al. (19) found no association between ADHD and SUD after adjusting for the presence of CD in a cross-sectional community-based sample of adolescents. Moreover, in a school sample of 11-15 year old, Molina et al. (20) found that ADHD comorbid with CD were associated with elevated substance use over ADHD alone and CD alone.

Although methodological differences in characteristics of the samples assessed, such as age, origin of the sample (clinical or communitarian) and history of ADHD treatment might contribute to these controversial results among studies, it is important to note that adolescent SUD is a very heterogeneous condition (1). In such a context, more than one etiological model might be implicated. Besides, few investigations have addressed the association between ADHD and SUD in other cultures despite the potential cross-cultural variability in the deviance of illegal drug use and the consistent worldwide prevalence of ADHD (21). For instance, the ADHD prevalence was estimated in 5.8 % in the South of Brazil (22). Thus, the goal of our study was to evaluate whether ADHD was associated with SUD, controlling for the effect of CD, in a community-based sample of Brazilian adolescents.

METHODS

Data were collected in the city of Canoas, an industrial suburb surrounding the Brazilian southernmost state capital (Porto Alegre). Canoas has an estimated population of 329,174 inhabitants (23).

This was a community-based, case-control study where the independent variable was presence of ADHD and the dependent variable was a current diagnosis of either abuse or dependence of marijuana, cocaine and/or inhalants. These three drugs are the most common illicit drugs used in Brazil, where heroin use is quite rare (2). This project was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre. Written informed consent was obtained from all participants and their parents.

Screening procedures

The sample was recruited from a delimited area served by four public health clinics that have data from all families living inside the area. We obtained addresses of all male adolescents born between 1984 and 1990 from their files (n = 1,409). Consulting the heath clinics files was the best way of assessing all residents of the selected area; to be in the health clinic's file, the individual needed to live inside the area, not necessarily to be a patient at the health clinic (that is, the list was not a medical record).

Based on a previous sample size calculation [$\alpha = 0.05$; study power $\cong 0.80$; odds ratio = 3, discordant pairs = 29 (prevalence of ADHD in adolescents with SUD = 30% and in adolescents without SUD = 4%)], we estimated needing a sample size of 90 pairs of cases and controls. Considering a 6 % prevalence of SUD in the community (24), we needed to screen 1500 adolescents. To make data collection feasible in the community, we decided to decrease the ratio of cases/controls from 1:1 to 1:3 (60 cases and 180 controls). This allowed us to reduce the number of adolescents to be visited in the community to approximately 1,000.

Trained research assistants (RAs) applied a screening instrument to detect SUD, using the Brazilian version (25) of the *Alcohol Smoking and Substance Screening Test* (ASSIST)

(26). The ASSIST evaluates patterns of use of nicotine, alcohol, marijuana, cocaine, inhalants and other substances in the last three months, generating scores suggestive of abuse (4-15) and dependence (16-20) for each drug. A subject was considered as screening positive (SP) if he had a score in the ASSIST ≥ 4 for marijuana, cocaine or inhalants. In order to be considered screening negative (SN), a subject should have presented a score < 4 for all substances (the only exception accepted was a score ≥ 4 for nicotine). Considering a cutoff score ≥ 4, the Brazilian version of the ASSIST (25) had sensitivity ranging from 84-91%, specificity ranging of 79-98%, positive predictive value between 80-93% and negative predictive value ranging from 85-96%, depending on each substance. The ASSIST was administered to the adolescents in their homes.

The SP subjects were further evaluated according to inclusion and exclusion criteria for the case-control protocol. In order to be eligible, the SP subjects were required to be 15 to 20 years of age, male and have a diagnosis of abuse or dependence of marijuana, cocaine or inhalants based on the drug section of the *Mini International Neuropsychiatry Interview* (MINI) (27). This instrument generates psychiatric diagnoses based on DSM-IV criteria and has good and well described psychometric properties (28). To be eligible as a control, the SN subjects were required to be male at the same age range and have negative (current and lifetime) diagnoses of abuse or dependence of illicit drugs and alcohol in the MINI. The exclusion criteria for both groups were the absence of an adult to inform about possible childhood psychopathology and patients clinically unable to answer questions (presence of mental retardation and/or psychosis). The entire sample, despite the age or being a case or a control, underwent absolutely the same diagnostic procedures.

We visited 968 houses to find 66 (6.81%) adolescents classified as SP and 545 (56.3%) youths as SN. The other 357 (36.9%) adolescents included were: 34 adolescents (3.5%) with ASSIST ≥ 4 only for alcohol (not eligible for any of the final groups), 13 (1.34%)

adolescents who refused to be interviewed, 37 (3.82%) youths that fulfilled exclusion criteria mentioned above and 273 subjects (28.2%) who were not found at home after 3 visits (one during the weekend).

From the 66 SP, 1 refused to participate, 2 met exclusion criteria and 2 did not fulfill SUD criteria according to MINI. Thus, 61 adolescents met our inclusion criteria and comprised the case group, from whom 5 had received previous treatment for SUD and all others had never received treatment for any psychiatric diagnosis. For each case, we selected three controls matched by age and proximity to the case's home (the three living nearest) from the entire group of SN. Two adolescents selected to comprise the control group refused to participate and another one moved to another city, so we replaced them. Using these procedures, we enrolled 183 subjects in the control group. Just one subject in this group had received psychiatric treatment (for depression) and all of them had a urinary test negative for marijuana and cocaine. In the entire sample, no subject had previous treatment for ADHD (medication, behavioral therapy or parental training skills).

Insert Figure 1 about here

Diagnostic Procedures

RAs administered the Brazilian version (29) of the *Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version* (K-SADS-E) (30) for those under the age of 18 years. Inter-rater reliability was confirmed previously (Kappa coefficient from 0.89 to 0.98; $p < 0.01$). For those who were 18 years old or older, RAs applied the MINI (27) (Kappa coefficient from 0.91-0.98; $p < 0.01$). Since the MINI does not fully cover child psychiatric diagnoses, the ADHD, CD, Oppositional Defiant Disorder

(ODD) and Separation Anxiety sections of the K-SADS-E were administered to these subjects. Interviews were conducted only with the parents. In addition, an experienced child psychiatrist (PI of the project) reassessed any positive psychiatric diagnosis derived from structured interviews for all enrolled subjects in clinical interviews with the parents, also evaluating its age of onset. The PI also re-interviewed all adolescents to investigate the pattern of drug consumption [age of first use, age of onset of abuse and/or dependence and months of regular use (at least once a week)]. Conduct symptoms were assessed with both adolescents and parents, and CD diagnosis was made based on a combination of both sources of information using an "or rule' (31).

For other psychiatric disorders, we computed lifetime diagnoses (including CD diagnosis). We also created a special group for each psychiatric diagnosis including only subjects for whom psychiatric disorders began before the onset of SUD *(BeSUD)*. This procedure conservatively assured that the disorder was not determined by the presence of the SUD.

ADHD severity was assessed by the SNAP-IV scale, which is a largely used measure in ADHD studies (32). This instrument is a 26-item scale based on DSM-IV ADHD and ODD symptoms, and items are scored from 0, *never*, to 3, *very often.* SNAP-IV was answered by subjects´ parents. Subjects' overall functioning was assessed by the *Clinical Global Assessment Scale* (CGAS). The CGAS is a widely used measure of child and adolescent overall functioning with adequate psychometric properties (33).

Demographic variables were systematically collected for all subjects during the screening phase (ethnicity, parent marital status, family density, parent and subject education, subject's religion practice and socioeconomic status). Religious practice was assessed since a previous study suggested its impact on SUD in Brazilian adolescents (34). S*ocioeconomic status (SES)* was defined using the scale from the Brazilian Association of Market Research

(35). This scale has five socioeconomic levels, from “A” (highest) to “E” (lowest). Estimated IQ was obtained from the Block Design and Vocabulary subtests of the *Wechsler Intelligence Scal*e – Third edition (WISC-III) (36), for adolescents under 17 years of age, and from the same subtests of the *Wechsler Adult Intelligence Scal*e (WAIS-III) for older youths (37). This is a used a standard strategy for estimating IQ in epidemiological studies (38-40).

Data Analyses

First, we compared patients with SUD to controls on demographic variables, estimated IQ, and psychiatric comorbidity. Second, we selected potential covariates based on conceptual analyses of the literature and/or a conservative statistical definition (association with both the study factor and outcome for a $p \leq 0.20$).

The difference between cases and controls in ADHD prevalence was assessed adjusting for potential covariates by conditional logistic regression analysis (CLR) (41). Since in our study each set of 1 case and 3 controls were previously matched according to pre-determined covariates, CLR was the best analysis model. This data analytic approach has been extensively used in studies with matching for covariates (42, 43). A significance level of 5% was accepted in all analyses.

RESULTS

Subjects’ demographic characteristics, estimated IQ and global functioning are shown in Table 1. Compared to the controls, the group of cases included significantly more African-

Brazilian subjects ($p = 0.001$), divorced biological parents ($p = 0.02$), and subjects with lower socioeconomic level ($p = 0.01$), educational level ($p < 0.01$), estimated IQ ($p < 0.01$) and global functioning ($p = 0.01$).

Insert Table 1 about here

The pattern of drug use in adolescents with SUD can be found in Table 2. The most frequent SUD diagnosis was for marijuana (91.8%), followed by cocaine (34.62% snorted cocaine and 16.39% crack) and inhalants (9.83%). Approximately 50% of the probands had SUD for more than one illicit drug and 47.5% also had an AUD diagnosis (abuse=20, dependence=9). In the control group, 13 subjects (7.1%) had experimented with marijuana, 8 (4.4%) with cocaine, and 3 (1.6%) with inhalants. Nobody in the whole sample reported previous drug injection.

The most frequent lifetime (LT) diagnoses in SUD cases were CD (60.7%), followed by ADHD (44.3%) and Anxiety Disorder (24.6%). In 73% of the cases with CD, CD was present before the diagnosis of SUD (BeSUD); in the control group, most frequent LT diagnoses were Anxiety Disorder (14.8%), ODD (9.3%) and ADHD (7.7%) (Table 3). Only ADHD and CD were significantly more prevalent in cases than in controls either for LT diagnoses and BeSUD criterion ($p<0.01$ for all of them). Regarding ADHD severity, the mean SNAP-IV score was 42.93 (SD=13.14) for cases and 33.71 (SD=10.05) for controls. The mean number of lifetime conduct symptoms among cases with CD LT was 5.57 (SD=2.32), 5.37 (SD=2.38) for cases with CD BeSUD and 5.36 (SD=2.35) among controls with CD. With regard to ADHD+CD comorbidity, of the 27 ADHD cases, 23 (85%) had CD LT and 16 (59%) had CD BeSUD. In the control group, 7 of the 14 ADHD subjects (50%) had a CD diagnosis.

Insert Table 3 about here

The following variables were associated with both SUD and ADHD for a $p \leq 0.2$: estimated IQ, schooling, ethnicity, religion, ADHD, CD (both LT and BeSUD). We decided not to include schooling in the model to avoid over-controlling, since it was highly associated with IQ (r=0.58; p = 0.01).

As can be seen in Table 4, ADHD was strongly associated with SUD (OR=9.12; p<0.01; $CI_{95\%}$=2.84-29.31) even after adjusting for the above-mentioned covariates, which included CD BeSUD. As expected, CD BeSUD was also strongly associated with SUD in this model (OR=8.0; p<0.01; $CI_{95\%}$ =2.34-27.39). In addition, ADHD was also significantly associated to SUD if CD LT was entered in the model instead of CDBeSUD (ADHD: OR=5.86; p=0.01; $CI_{95\%}$=1.51-22.72 and CD LT: OR=19.57 p<0.01; $CI_{95\%}$=4.17-91.87).

Insert Table 4 about here

We also analyzed separately the impact of the inattentive and hyperactivity/impulsivity dimensions of the ADHD diagnosis (inattentive and hyperactivity/impulsivity dimensions of SNAP-IV) on SUD. After adjusting for potential confounders, inattentive dimension was associated with a higher likelihood of SUD (OR=1.14; p<0.01; $CI_{95\%}$=1.06-1.22), as was the hyperactivity/impulsivity dimension (OR=1.14; p<0.01; $CI_{95\%}$=1.06-1.22).

DISCUSSION

In this study, we found an association between childhood ADHD and male adolescent abuse or dependence of illicit SUD. The presence of ADHD was associated with a significantly higher OR for SUD, even when results were adjusted for the effect of CD and other potential confounders. To the best of our knowledge, this is the first study outside of the US reporting such findings in a community sample of male adolescents with illicit SUD.

First, our findings are in agreement with an extensive literature documenting an association of CD and SUD in adolescents (6, 7). One major criticism about cross-sectional studies suggesting the association between CD and SUD refers to difficulties in disentangling the direction of the relation, since conduct symptoms might be exacerbated by, or the result of SUD (44). In our study, CD was associated with SUD even when diagnosis was restricted to those patients presenting it before fulfilling DSM-IV criteria for illicit SUD.

Our results documenting an association between ADHD and SUD in adolescents concur with recent findings from the literature (17, 45). Several investigations refute an independent effect of childhood ADHD on adolescent SUD (8, 19). King and associates (46) did not find an effect of ADHD on advanced use of marijuana in a community sample of 14-year olds, although there was an effect of ADHD in the analysis on initial use by age 14, suggesting a contribution of ADHD symptoms on early substance use Disney and colleagues (19) did not find effects of ADHD that were independent of CD. The integration of these findings is virtually impossible due to extreme diversity in methodology among studies. Some important methodological issues might have contributed for the contradictory findings in studies trying to disentangle the role of ADHD on SUD in adolescents, such as: a) differences in age range and gender assessed [for instance, while our sample was comprised only by male gender with subject's mean age = 17.84 years, some studies reporting absence of association

(8, 46) either enrolled both genders or assessed younger subjects]; b) different definitions for the outcomes related to drugs (use, misuse, abuse, dependence, or abuse plus dependence); c) absence of controlling for the effect of ADHD treatment (8, 19); d) no adjustment for the presence of CD in some studies (47); and e) the use of clinically- referred samples (8).

Besides methodological issues, our finding may have been influenced by the environmental context of our sample. None of the cases with ADHD had experienced treatment for their disorder, which could have resulted in progression of risk for SUD. This is a problem of lack of available treatment resources and lower level of recognition of the disorder in developing countries (21, 48), since our cases did not have low severity ADHD. Untreated samples of adolescents with ADHD may be more commonly found in less-developed countries, such as Brazil, than in USA or other developed countries. This is a relevant issue, as previous ADHD treatment may be associated with lower rates of SUD in samples of adolescents and adults (49).

Considering a developmental perspective for adolescent psychopathology, it makes clinical sense that ADHD might be a risk factor for SUD, independently of CD. ADHD is one of the psychiatric diagnoses with earlier age of onset. Some of the associated ADHD impairments through childhood and adolescence are consistently mentioned in the literature as enhancing the adolescent SUD liability, such as peer rejection and academic problems (50). In addition, children with ADHD may reach adolescence without enough coping strategies to deal with typical conditions associated with drug exposure in this stage of life, such as propensity to risk behavior, and mood switch (50). Thus, untreated ADHD could be a sufficient condition to a higher SUD liability, independent of an antisocial behavior.

From a neurobiological perspective, it is also not surprising that ADHD might be an early antecedent of SUD. Children with ADHD likely have dysfunctions in the dopaminergic circuits, mostly in basal ganglia and frontal cortex (51), with defects in executive function

(52) and in the reward system (53). It is well documented that basal ganglia and frontal areas are affected in SUD subjects (for a review, see ref. 54). Besides, executive (6, 7) and reward system functions (54) have a strong influence on SUD liability. Thus, children with ADHD have cognitive dysfunctions that may impair them in high-risk drug use situations, such as a positive illusory bias (i.e., a tendency to overestimate their performance or competence) (55) and in sustaining a behavior despite negative consequences (56). Although executive dysfunction is present in both CD and ADHD diagnoses, it was suggested that, comparatively, executive problems are more severe in ADHD diagnosis (52). Furthermore, ADHD and SUD have dysfunctions in the reward system (RS). The RS is associated with motivation, salience of a stimulus (57) and delay capacity (53). Subjects with SUD may chose behaviors with high immediate gains (e.g., “getting high” or sensation-producing activities) in spite of higher future losses such as the long term consequences of addiction or other adverse health effects (58). Finally, genetic studies suggest a heritability of approximately 33% (59) for illicit SUD and the effect of dopaminergic genes (60). There is a whole body of literature supporting the influence of dopaminergic genes in ADHD and in response inhibition (61, 62). Recently, it was documented that DAT1 gene variation (a strong candidate gene in ADHD) might influence the etiology of cocaine dependence (12).

Our findings have some limitations. Cases and controls were not perfectly matched, although we used conservative statistical approaches to adjust for the effect of covariates. We cannot extend our results to females or to adolescents with abuse or dependence of only alcohol and/or nicotine. Since our sample consisted of mostly marijuana or marijuana plus cocaine users, our results might not necessarily apply to adolescents with a different profile of SUD(s) or substance use. We collapsed the SUD diagnoses of abuse and dependence in one category, as has been done in several other investigations (17, 19), although abuse or dependence may reflect different SUD pathways. Also, we did not have enough power to

assess effects of ADHD subtypes on SUD. However, we documented independent effects of ADHD inattentive and hyperactive/impulsive dimensions on SUD. The research assistants, who applied the K-SADS-E, were blind to the goal of the study, but not to the subjects' status (case vs. control), since this would be difficult in a community study where subjects were assessed for SUD in their homes. Nevertheless, their reliability was previously assessed as adequate for both ADHD and CD. The assessment of psychiatric diagnoses was made retrospectively due to the cross sectional design of this study which may have determined recall bias (i.e., over reporting ADHD in the case group and/or underreporting ADHD in the control group). However, the ADHD prevalence in the control group was very similar to the one found previously in a school sample of young adolescents in the city of Porto Alegre (22). Finally, since this was a case-control study, we can only suggest an association between ADHD and SUD. A causal relation between them should be addressed by longitudinal studies.

The specific strengths of our study are: a) a community based sample; b) an extensive psychiatric diagnostic assessment including parental report (using both semi-structured and clinical interviews deriving DSM-IV diagnoses); c) ADHD treatment naive subjects in both groups; d) adjustment of the results for the presence of CD already present before the SUD onset; e) a sample from a culture outside of the US.

Despite the clear need for longitudinal studies on this issue, our results might have some practical applications for adolescent SUD prevention. A substantial literature documents the existence of effective treatments for ADHD (63) and some recent evidence suggests that the pharmacological treatment of ADHD might be associated with lower risks for SUD (49). Moreover, once ADHD begins in early childhood, before the onset of substance use, these at-risk children may be identified and targeted for early and ongoing intervention to prevent the onset of SUD (1).

Acknowledgments: The authors thank Toxilab for the urinary tests; Anelise Lusser, Franciny Port, Mariana Walcher, Paulo Eduardo Nunes and Thais Schaeffer (research assistants).

Funding sources: This work was partially supported by research grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil; governmental institution) (Grant 307780/2004-0), Hospital de Clínicas de Porto Alegre (Public University Hospital, linked to the Federal University of Rio Grande do Sul) and an unrestricted Grant from Eli-Lilly (pharmaceutical company).

REFERENCES

1. Bukstein OG, Bernet W, Arnold V, Beitchman J, Shaw J, Benson RS et al.: Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. J Am Acad Child Adolesc Psychiatry 2005; 44:609-21.

2. Galduroz JC, Noto AR, Nappo SA, Carlini EA: Household survey on drug abuse in Brazil: study involving the 107 major cities of the country--2001. Addict Behav 2005; 30:545-56.

3. Laumon B, Gadegbeku B, Martin JL, Biecheler MB; SAM Group: Cannabis intoxication and fatal road crashes in France: population based case-control study. BMJ 2005; Dec 10;331(7529):1371.

4. Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W: Cannabis use and mental health in young people: cohort study. BMJ 2002; 325:1195-8.

5. World Health Organization (WHO): available at http://www.who.int/substance_abuse/facts/cannabis/en/index.html (assessed January 08, 2006).

6. Tarter RE, Kirisci L, Mezzich A, Cornelius JR, Pajer K, Vanyukov M et al.: Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. Am J Psychiatry 2003; 160:1078-85.

7. Clark DB, Cornelius JR, Kirisci L, Tarter RE: Childhood risk categories for adolescent substance involvement: a general liability typology. Drug Alcohol Depend 2005; 77:13-21.

8. Biederman J, Wilens T, Mick E, Faraone SV, Weber W, Curtis S et al.: Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 1997; 36:21-9.

9. Biederman J, Newcorn J, Sprich S: Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. Am J Psychiatry 1991; 148:564-77.

10. Souza I, Pinheiro MA, Denardin D, Mattos P, Rohde LA: Attention-deficit/hyperactivity disorder and comorbidity in Brazil: comparisons between two referred samples. Eur Child Adolesc Psychiatry 2004; 13:243-8.

11. Todd RD, Huang H, Smalley SL, Nelson SF, Willcutt EG, Pennington BF et al: Collaborative analysis of DRD4 and DAT genotypes in population-defined ADHD subtypes. J Child Psychol Psychiatry. 2005; 46:1067-73.

12. Guindalini C, Howard M, Haddley K, Laranjeira R, Collier D, Ammar N et al: A dopamine transporter gene functional variant associated with cocaine abuse in a Brazilian sample. Proc Natl Acad Sci U S A. 2006; 21; 103:4552-7.

13. Shao C, Li Y, Jiang K, Zhang D, Xu Y, Lin L et al: Dopamine D4 receptor polymorphism modulates cue-elicited heroin craving in Chinese. Psychopharmacology. 2006; 186:185-90.

14. Horner BR, Scheibe KE: Prevalence and implications of attention-deficit hyperactivity disorder among adolescents in treatment for substance abuse. J Am Acad Child Adolesc Psychiatry 1997; 36:30-6.

15. Gittelman R, Mannuzza S, Shenker R, Bonagura N: Hyperactive boys almost grown up. I. Psychiatric status. Arch Gen Psychiatry 1985; 42:937-47.

16. Mannuzza S, Klein RG, Bonagura N, Malloy P, Giampino TL, Addalli KA Hyperactive boys almost grown up. V. Replication of psychiatric status. Arch Gen Psychiatry 1991; 48:77-83.

17. Molina BS, Pelham WE: Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. J Abnorm Psychol 2003; 112:497-507.

18. Tapert SF, Baratta MV, Abrantes AM, Brown SA: Attention dysfunction predicts substance involvement in community youths. J Am Acad Child Adolesc Psychiatry 2002; 41:680-6.

19. Disney ER, Elkins IJ, McGue M, Iacono WG: Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. Am J Psychiatry 1999; 156:1515-21.

20. Molina BSGM, Smith BH, Pelham WE: Interactive effects of Attention Deficit Hyperactivity Disorder and Conduct Disorder on early adolescent substance use. Psychology of Addictive Behs 1999; 13:348-358.

21. Rohde LA, Szobot C, Polanczyk G, Schmitz M, Martins S, Tramontina S: Attention-deficit/hyperactivity disorder in a diverse culture: do research and clinical findings support the notion of a cultural construct for the disorder? Biol Psychiatry 2005; 57:1436-41.

22. Rohde LA, Biederman J, Busnello EA, Zimmermann H, Schmitz M: ADHD in a school sample of Brazilian adolescents: a study of prevalence, comorbid conditions and impairments. J Am Acad Child Adolesc Psychiatry 1999; 38:716-722.

23. Instituto Brasileiro de Geografia e Estatística (IBGE): available at http://www.ibge.gov.br/ (assessed February 12, 2006).

24. Organização das Nações Unidas para Educação, Ciência e Tecnologia (UNESCO). 2002.

25. Henrique IF, De Micheli D, Lacerda RB, Lacerda LA, Formigoni ML: Validation of the Brazilian version of Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)] Rev Assoc Med Bras 2004; 50:199-206.

26. WHO ASSIST Working Group: The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction 2002; 97:1183-94.

27. Amorim P: Mini International Neuropsychiatric Interview (MINI): Validação de entrevista breve para diagnóstico de transtornos mentais. Revista Bras Psiquiatr 2000; 22:106-115.

28. Sheehan DV, Lecrubier Y, Sheehan KH, Janavs J, Weiller E, Keskiner A et al.: European Psychiatry. 1997; 12(5): 232-241.

29. Mercadante MT, Asbarch F, Rosário MC, Ayres AM, Ferrari MC, Assumpção FB et al.: K-SADS, 1º edição. São Paulo, SP: Protoc – Hospital das Clínicas da FMUSP; (1995).

30. Orvaschel H, Puig-Antich J: Schedule for Affective Disorders and Schizophrenia for School-Age Children: Epidemiologic, 4th Version. Ft. Lauderdale, FL: Nova University, Center for Psychological Study.

31. Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM: Best estimate of lifetime psychiatric diagnosis: a methodological study. Arch Gen Psychiatry 1982; 39(8):879-83.

32. Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB et al.: Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 2001; 40(2):168-79.

33. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H et al.: A children's global assessment scale (CGAS). Arch Gen Psychiatry 1983; 40:1228-31.

34. Dalgalarrondo P, Soldera MA, Correa Filho HR, Silva CA: Religion and drug use by adolescents. Rev Bras Psiquiatr 2004; 26:82-90.

35. Associação Brasileira de Empresas de Pesquisas. Critério de Classificação Econômica Brasil: available at http://www.anep.org.br/codigosguias/CCEP.pdf (assessed April 18, 2005).

36. Wechsler D: WISC-III/Manual. New York, NY: The Psychological Corporation. 1991

37. Wechsler D: Manual of the Wechsler Adult Intelligence Scale (3rd edition). San Antonio TX: The Psychological Corporation. 1997.

38. Silverstein AB: Two- and four-subtest short forms of the WAIS-R: a closer look at validity and reliability. J Clin Psychol. 1985; 41(1):95-7.

39. Brooker BH; Cyr JJ: Tables for clinicians to use to convert WAIS-R short forms. J Clin Psychol. 1986; 42:983-986.

40. Sattler J: Assessment of Children. 3rd ed. San Diego, CA: J Satter, 1988.

41. Hosmer D, Lemeshow S: Applied logistic regression. Hoboken, NJ: Wiley-Interscience. 2000.

42. Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R et al: Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet. 2006; 368(9546):1495-502.

43. Schmitz M, Denardin D, Silva TL, Pianca T, Roman T, Hutz MH et al: Association between alpha-2a-adrenergic receptor gene and ADHD inattentive type. Biol Psychiatry 2006 15;60(10):1028-33.

44. Dennis ML, Godley SH, Titus JC: Co-occurring psychiatric problems among adolescents: variations by treatment, level of care, and gender. TIE communiqué 5-8; http://www.treatment.org/communique/CHIPtreatment.pdf (assessed April 12, 2006).

45. Molina BS, Bukstein OG, Lynch KG: Attention-deficit/hyperactivity disorder and conduct disorder symptomatology in adolescents with alcohol use disorder. Psychol Addict Behav 2002; 16:161-4.

46. King SM, Iacono WG, McGue M: Childhood externalizing and internalizing psychopathology in the prediction of early substance use. Addiction 2004; 99:1548-59.

47. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M: Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. Arch Gen Psychiatry 1993; 50:565-76.

48. Rohde LA: ADHD in Brazil: the DSM-IV criteria in a culturally different population. J Am Acad Child Adolesc Psychiatry 2002; 41(9):1131-3.

49. Wilens TE, Faraone SV, Biederman J, Gunawardene S: Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 2003; 111:179-85.

50. Tarter RE: Etiology of adolescent substance abuse: a developmental perspective. Am J Addict. 2002; 11:171-91.

51. Seidman LJ, Valera EM, Makris N: Structural brain imaging of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005; 57:1263-72.

52. Fischer M, Barkley RA, Smallish L, Fletcher K: Executive functioning in hyperactive children as young adults: attention, inhibition, response perseveration, and the impact of comorbidity. Dev Neuropsychol 2005; 27:107-33.

53. Sonuga-Barke EJ: Psychological heterogeneity in AD/HD--a dual pathway model of behaviour and cognition. Behav Brain Res 2002; 10:29-36.

54. Volkow ND, Fowler JS, Wang GJ: The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology 2004; 47 3-13.

55. Gerdes AC, Hoza B, Pelham WE: Attention-deficit/hyperactivity disordered boys' relationships with their mothers and fathers: child, mother, and father perceptions. Dev Psychopathol 2003; 15:363-82.

56. Nigg JT, Casey BJ: An integrative theory of attention-deficit/ hyperactivity disorder based on the cognitive and affective neurosciences. Dev Psychopathol 2005; 17:785-806.

57. Kalivas PW, Volkow ND: The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005; 162:1403-13.

58. Bechara A, Martin EM: Impaired decision-making related to working memory deficits in individuals with substance addictions. Neuropsychology 2004; 18:152-62.

59. True WR, Heath AC, Scherrer JF, Xian H, Lin N, Eisen SA, Lyons MJ, Goldberg J, Tsuang MT: Interrelationship of genetic and environmental influences on conduct disorder and alcohol and marijuana dependence symptoms. Am J Med Genet 1999; 88:391-7.

60. Czoty PW, Nader MA: PET imaging of dopamine D2 receptors in monkey models of cocaine abuse: genetic predisposition versus environmental modulation. Am J Psychiatry 2005; 162:1473-82.

61. Aron AR, Poldrack RA: The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 2005; 57:1285-92.

62. Sergeant J: Are we ready for endophenotypes in attention deficit hyperactivity disorder? Rev. Bras. Psiquiatr. 2005; 4: 262-263.

63. Pliszka SR, Greenhill LL, Crismon ML, Sedillo A, Carlson C, Conners CK et al.: The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Attention-Deficit/Hyperactivity Disorder. Part II: Tactics. Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 2000; 39:920-7.

Table 2 (1) - Demographic characteristics, estimated IQ and global functioning in probands and controls

Characteristic	Cases (N=61)		Controls (N=183)		P value
	% (n)	Mean (SD)	%	Mean (SD)	
Age		17.84 (1.69)		17.86 (1.67)	0.45
Ethnicity					
-European-Brazilian	63.9 (39)		83.4 (153)		0.001
-African-Brazilian	36.1 (22)		16.4 (30)		
Divorced biological parents	49.2 (30)		32.8 (60)		0.02
Family density		4.37 (1.73)		4.39 (1.42)	0.9
SES* - A, B or C	45.9 (28)		62.8 (115)		0.01
Mother's schooling		5.68 (2.87)		6 (3.1)	0.21
Subject's schooling		7.18 (2.14)		8.87 (2.28)	<0.01
Affiliated to a religion	18.0 (11)		26.8 (49)		0.16
Estimated IQ **		84.48 (13.36)		93.29 (12.63)	<0.01
CGAS***		50.90 (11.85)		80 (6.98)	0.01

*Socioeconomic Status; **Quocient of inteligency; ***Clinical Global Assessment Scale

Table 3 (2) - Drug use in proband group (N=61)

	Marijuana (N = 56)		**Cocaine (snorted)** (N = 22)		**Crack** (N = 10)		**Inhalants** (N = 6)	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Age of experimentation	13.74 (1.83)		15.22 (1.60)		15.89 (1.90)		13.03 (2.49)	
Age SUD onset	14.44 (1.66)		16.0 (1.38)		15.7 (1.90)		12.33 (2.25)	
Subjects with Abuse		24		13		2		4
Subjects with Dependence		32		9		8		2

Table 4 (3) - Prevalence of psychiatric diagnosis in probands and controls

Psychiatric diagnosis	Probands (n=61) Percent (n)	Controls (n=183) Percent (n)	P Value
ADHD lifetime (LT)	44.3 (27)	7.7 (14)	<0.01
Conduct Disorder			
LT	60.7 (37)	6.0 (11)	<0.01
Onset BeSUD	44.3 (27)	NA	<0.01
Oppositional Defiant Disorder			
LT	14.8 (9)	9.3 (17)	0.24
Onset BeSUD	9.8 (6)	NA	0.96
Anxiety Disorder (AD)			
LT	24.6 (15)	14.8 (27)	0.08
Onset BeSUD	21.3 (13)	NA	0.22
Mood Disorder (MD)			
LT	14.8 (9)	6.6 (12)	0.058
Onset BeSUD	8.2 (5)	NA	0.6
Other comorbidities (OC)			
LT	0	3.3 (8)	0.21

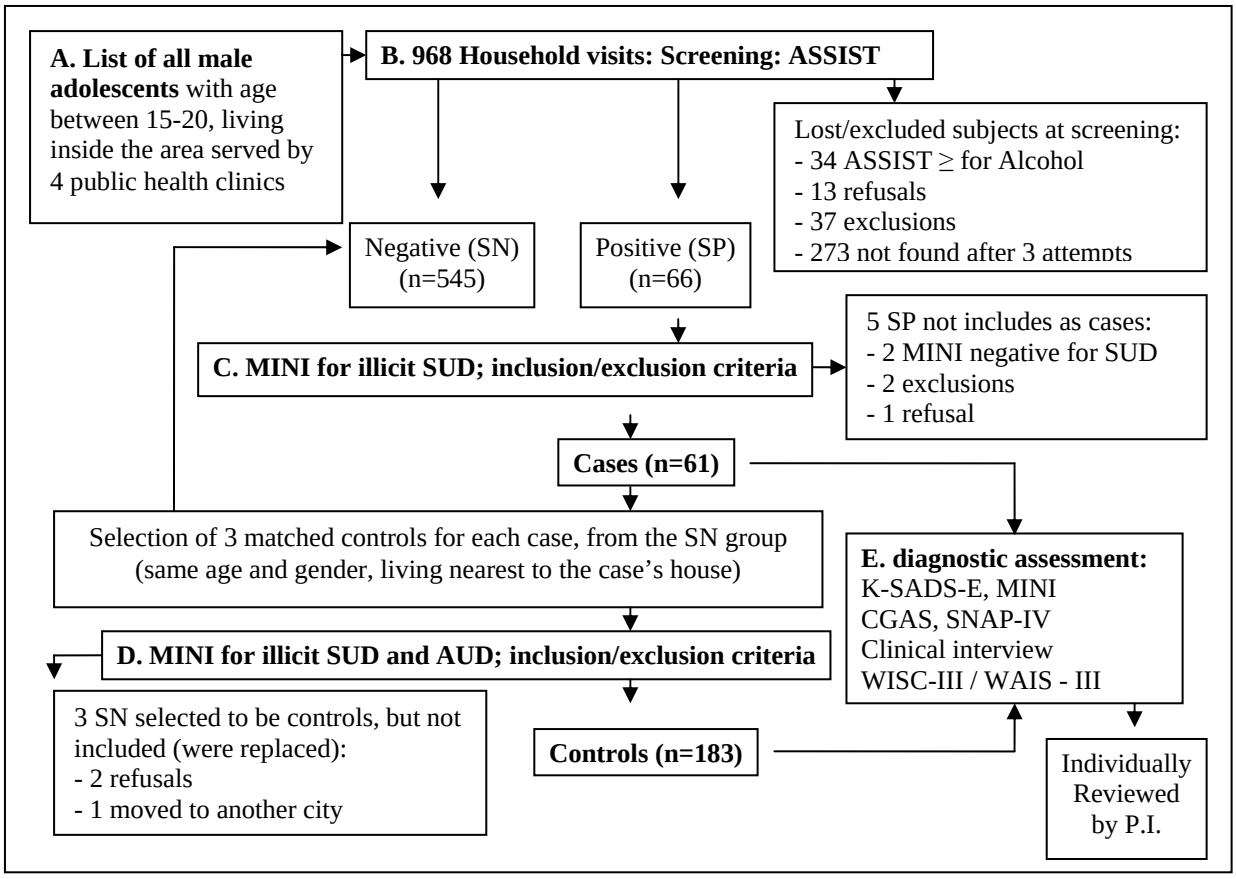
AD: separation anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, social phobia, specific phobia, generalized anxiety and panic disorder. MD: dysthimia, major depression and bipolar disorder. OC: enuresis and stutter. NA = not applicable.

Table 5 (4) - Odds ratio (OR) for SUD according to the presence of ADHD, adjusted for potential covariates

	OR	Wald	P value	95% CI	
				Lower	Upper
ADHD- LT	9.12	13.76	<0.01	2.84	29.31
CD BeSUD	8.00	10.99	<0.01	2.34	27.39
Ethnicity	3.28	4.74	.03	1.13	9.58
Estimated IQ	.97	3.74	.05	.93	1.00
Religion	.88	.05	.83	.28	2.79

SUD = Illicit substance use disorder; ADHD LT = Attention deficit/hyperactivity Disorder, lifetime; CD BeSUD = Conduct disorder diagnosis present before the onset of SUD; IQ = intelligence quotient.

Figure 1 - Flow chart for the selection of cases and controls



Note: ASSIST = Alcohol Smoking and Substance Screening Test; MINI = Mini International Neuropsychiatry Interwiew; SUD = Substance Use Disorder; K-SADS-E = Schedule for Affective Disorders and Schizophrenia for Scholl-Age Children-Epidemiological Version; CGAS = *Clinical Global Assessment Scale*. WISC-III = *Wechsler Intelligence Scale* – 3ª edição; WAIS = *Wechler Adult Intelligence Scale* (WAIS-III); P.I = Principal Investigator.

6 ESTUDO 2 - QUESTÃO DE PESQUISA

Qual a efetividade do MFD-SODAS nos sintomas de TDAH em adolescentes com TDAH e TUSP?

ARTIGO PRINCIPAL 2

Methylphenidate-SODAS improves Attention-Deficit/ Hyperactivity Disorder symptoms in adolescents with Substance Use Disorder: a randomized crossover clinical trial

In press, Brazilian Journal of Medical and Biological Research

Methylphenidate-SODAS improves Attention-Deficit/ Hyperactivity Disorder symptoms in adolescents with Substance Use Disorder: a randomized crossover clinical trial

CM Szobot[1,2,3], MD; LA Rohde[2], MD, PhD; B Katz[2]; P Ruaro[1,3]; T Schaefer[1,3]; M Walcher[1,3]; O Bukstein[4], M.D; F Pechansky[1], MD, PhD.

[1]Centro de pesquisas em Álcool e Drogas, Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul, Brasil (UFRGS). [2]Programa de Déficit de Atenção/Hiperatividade, HCPA, UFRGS, Brasil. [3]Universidade Luterana do Brasil, Curso de Medicina, Brasil. [4]Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, USA

Running Title: Methylphenidate in adolescents with ADHD and drug use.

Corresponding author: Claudia M. Szobot. Centro de Pesquisa em Álcool e Drogas, Universidade Federal do Rio Grande do Sul. Hospital de Clínicas de Porto Alegre. Address: Rua Ramiro Barcelos, 2350. CEP: 90035-003. Porto Alegre, RS, Brazil. Phone/fax: 55-51-3330-5813. **e-mail:** cmszobot@terra.com.br

Disclosure: this work was partially supported by research grants from: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) (Grant 307780/2004-0); Hospital de Clínicas de Porto Alegre (financial support for placebo and subject transportation). Toxilab® provided urinary assays. Medication was provided by NOVARTIS at no cost and without restrictions.

Word count: 2,585

Number of Tables and Figures: 2 Tables and 2 Figures

Last revision: 16/11/07

ABSTRACT

Objectives: To evaluate the effectiveness of a long-acting formulation of methylphenidate (MPH-SODAS) on Attention-Deficit/ Hyperactivity Disorder (ADHD) symptoms in an outpatient sample of adolescents with ADHD and Substance Use Disorders (SUD). Secondary goals were to evaluate the tolerability and impact of MPH-SODAS on drug use. *Method:* This was a 6-week, single-blind, placebo-controlled crossover study assessing efficacy of escalated doses of MPH-SODAS on ADHD symptoms in 16 adolescents with ADHD/SUD. Participants were randomly allocated to either group A (weeks 1-3 on MPH-SODAS, weeks 4-6 on placebo) or group B (reverse order). The primary outcome measures were the Swanson, Nolan and Pelham Scale - version IV (SNAP-IV) and the Clinical Global Impression Scale (CGI). We also evaluated MPH-SODAS adverse events through the Barkley Side Effect Rating Scale (SERS) and subjects' reports of drug use during the study. *Results:* The sample was comprised by marijuana (n=16; 100%) and cocaine users (n=7; 43.8%). Subjects had a significantly higher reduction in the SNAP-IV and CGI scores ($p<0.001$ for all analyses) during MPH-SODAS treatment when compared to placebo. No significant effects for period and sequence were found in analyses with the SNAP-IV and CGI scales. There was no significant effect over drug use. MPH-SODAS was well-tolerated, but it was associated with more severe appetite reduction than placebo ($p<0.001$). *Conclusions:* MPH-SODAS was more effective than placebo in reducing ADHD symptoms in a non-abstinent outpatient sample of adolescents with comorbid SUD. Randomized clinical trials, with larger samples and SUD intervention are recommended.

Keywords: ADHD, methylphenidate, substance use disorder, treatment, adolescents.

INTRODUCTION

Adolescent substance use disorder is a major mental health concern in different cultures[1,2]. Marijuana is the most abused illicit drug worldwide, with an annual prevalence of 2.5% and affecting mostly young populations[3]. The use of cocaine is also increasing during adolescence, particularly in developing countries[2]. The worldwide prevalence of Attention Deficit/Hyperactivity Disorder (ADHD) in adolescents was recently estimated by our group in a meta-analysis of the literature (2.74; $CI_{95\%}$ = 2.04-3.45)[4]. These figures are even higher in non-referred samples from developing countries[5, 6]. The prevalence rates and associated impairments also qualify ADHD as a major public health concern[7].

The ADHD is highly prevalent among adolescents with Substance Use Disorders (SUD)[8, 9]. The comorbidity is clinically relevant, since ADHD is associated with both earlier and more frequent alcohol relapses[10] and lower likelihood of cannabis treatment completion[11] in adolescents. Several evidence-based guidelines suggested that stimulants (e.g.,methylphenidate - MPH) should be the first option for treatment of ADHD (see, for instance, Pliska et al[12]). However, ADHD treatment studies typically exclude individuals with drug use/misuse or SUD. Given that most abused drugs act on dopaminergic system[13], as does MPH[14], pharmacological studies of subjects with ADHD/SUD are crucial.

Few open trials with bupropion[15, 16] and one randomized clinical trial (RCT) with pemoline[17] addressed adolescents with ADHD/SUD. All of them reported significant treatment effects in reducing ADHD symptoms. Interestingly, first line medications for ADHD were recently evaluated in adults with the comorbidity, with a positive result over ADHD symptoms[18], and the few available RCTs did not find a superior effect of MPH over placebo[19, 20], or over placebo and bupropion[21] in ADHD symptoms. These findings may not

necessarily be translated to adolescents, since there are reports of different MPH[22] and drug responses[23-25] between adults and adolescents. Thus, the main goal of this study was to evaluate the effectiveness of a long-acting formulation of MPH (MPH-SODAS) in reducing ADHD symptoms in adolescents with ADHD/SUD, comparatively with placebo. Secondarily, we evaluated drug consumption and MPH-SODAS tolerability.

METHODS

Study design and participants

This was a 6-week, randomized, single-blind, placebo-controlled crossover trial assessing effects of MPH-SODAS on ADHD symptoms in 16 outpatient male adolescents with both ADHD/SUD. Subjects were randomly allocated to two groups. Group A received MPH-SODAS while group B received placebo (PLA) in the first three weeks. In weeks 4-6, group A received PLA and group B received MPH-SODAS. The study was conducted between November and December, 2005 in the city of Porto Alegre (capital of Brazilian Southernmost State, Rio Grande do Sul). Figure 1 summarizes study design and procedures.

Please insert Figure 1 about here

The project was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre (approved as an IRB by the Office for Human Research Protections, United States of America - IRB 00000921). Written informed consent was obtained from all

participants and their parents. Subjects were recruited from a previous community case-control study assessing adolescents with ADHD/SUD (Szobot et al., *submitted*). From the 21 eligible subjects, 11 accepted to be enrolled in the study. We also recruited more subjects by advertisements in local newspapers and radio broadcasts; from this source, we screened 15 adolescents. Eleven youths had ADHD/SUD; however 3 subjects met exclusion criteria (see below) and 3 refused to participate. The other 5 adolescents were included in the study, thus comprising our total sample size of 16 subjects. Inclusion criteria were age range between 15 and 21 years-old, male gender, current diagnosis of abuse or dependence of marijuana or cocaine, current diagnosis of ADHD and stimulant-naive subjects. Exclusion criteria were the lack of a responsible adult to inform about possible childhood psychopathology or to take responsibility for the medication, the need for inpatient treatment for drug abuse or psychiatric comorbidities, and the presence of a primary psychiatric condition that required immediate outpatient treatment (like moderate/severe depression). SUD treatment was not provided. Drug and alcohol abstinence was not required for study eligibility.

Study medication procedures

A pharmacist packaged MPH-SODAS and matching PLA in capsules, so that MPH-SODAS and PLA could not be visually differentiated. One of the investigators (LAR) randomized the 16 subjects into groups A or B, and prepared weekly blisters of medications for each participant. MPH-SODAS is suitable for crossover designs since its clinical response is limited to no more than 8-9 hours[26], avoiding carryover effects.

The medication was given to the subjects' mothers, and was taken once a day (in the morning), by oral administration. Study compliance was assessed by self-report, mother's report and pill counting. Doses used in each week are described in Figure 1.

Diagnostic Procedures

The diagnoses of ADHD and comorbid mental disorders were confirmed by semi – structured interviews (*Schedule for Affective Disorders and Schizophrenia for School – Age Children, Epidemiological Version – K-SADS-E)* with the parents, and clinical interviews with the adolescent and the parents conducted by a child psychiatrist (CMS). Detailed description of the diagnostic process in our ADHD clinic can be found elsewhere[27]. The diagnoses of SUD relied on the drug section of the *Mini International Neuropsychiatry Interview* (MINI), Brazilian version[28], which generates diagnoses of abuse or dependence according to DSM-IV criteria. All participants had drug use confirmed by urinary tests (cannabis and/or cocaine). Other measures were: a) the *Clinical Global Assessment Scale*[29] (CGAS); b) the *Brazilian Association of Market Research Form*[30] for evaluation of socioeconomic status (SES); c) Block Design and Vocabulary subtests of the *Wechsler Intelligence Scal*e – Third edition[31] (WISC-III) (Wechsler, 1991) and the *Wechsler Adult Intelligence Scal*e[32] (WAIS) for estimation of IQ.

Outcome measures: Efficacy Assessments

The primary outcome measures (efficacy assessment) were the *Swanson, Nolan and Pelham Scale – version IV*[33] *(SNAP-IV)* and the *Clinical Global Impression Scale*[34] (CGI)

(Severity, Clinical improvement and Efficacy scores) (National Institute of Mental Health, 1985). The *SNAP-IV* is a 26-item scale, based on DSM-IV ADHD and Oppositional Defiant Disorder (ODD) symptoms. Items are scored on a 4-point scale (from 0, *never*, to 3, *very often*). In the present study, the SNAP-IV evaluation was based on the mother's report. The CGI scale is an investigator-rated scale which comprises 3 subscales: severity, clinical improvement and efficacy. *The CGI severity* consists of a 7-item scale (from 0, not evaluated, to 7, extremely ill). The *CGI clinical improvement* is also a 7-item scale (from 0, *not evaluated*, to 7, *much worst*) and the *CGI efficacy* combines adverse events with clinical improvement (from 1, *no adverse effect/notable clinical improvement*, to 16, *adverse effect is higher than beneficial effects/ no clinical improvement/clinically wors*e).

With regard to secondary outcome measures, drug use was evaluated by the *number of days with drug use* (weekly), the *number of smoked cannabis cigarettes* (weekly) and by *urinary test for cannabis and cocaine* (weeks 3 and 6). Tolerability consisted of the total score of the *Barkley Side Effect Rating Scale*[35] (SERS), and on its insomnia, headache and appetite subitems.

Data analyses

Analyses of primary and secondary outcome measures were performed using a Mixed-Effects Model (MEM) approach which provides a flexible framework for the analysis of repeated measures while accounting for missing data (i.e., lost to follow-up)[36]. We used treatment, period, sequence and dose-within-treatment as fixed variables, baseline measures as covariates (excepts for CGI clinical improvement and efficacy, which does not have baseline values) and subjects as a random variable. For each analysis, the best covariance

structure fitting the data was selected using Akaike's Information Criterion (AIC)[37]. A significance level of 5% was set for all analyses.

RESULTS

Two participants, both from group A, dropped from the study. One of them started an intense use of inhalants, requiring hospitalization, by the end of the third week. The other one felt worst (more restless) during the forth week, and dropped out from the study (dropout out rate = 12.5%).

Sample characteristics

All subjects had a cannabis SUD diagnosis (approximately 3 years of regular use) and 7 (43%) also had cocaine abuse or dependence (current or past). With regard to current diagnosis of cocaine, one subject from group A had abuse and one had dependence. From group B, 2 adolescents had current abuse and one had dependence. In addiction, 5 (31.3%) adolescents had an Alcohol Use Disorder (AUD). Subjects' mean SNAP-IV and CGAS baseline scores were, respectively, 50.63 (SD=13.76) and 42.19 (SD=9.12). The most common type of ADHD was the combined (n=12, 75%), followed by the inattentive (n=3, 18.75%) and the hyperactive/impulsive type (n=1). Besides ADHD and SUD, 14 subjects (87.5%) had an additional (current or lifetime) diagnosis of Conduct Disorder, 5 (31.25%) of ODD, 3 (18.75%) of Major Depression and one of Separation Anxiety (this last subject

belonged to group 2). Socio-demographical characteristics, estimated IQ, psychiatric disorders, ADHD severity and drug use of the sample according to the group randomization can be found in Table 1. There were no significant differences in all these variables according to sequence (comparison between subjects receiving MPH or placebo in the first period) ($p > 0.05$).

Please insert Table 1 about here

Primary outcome measures: SNAP-IV and CGI

The MEM analyses revealed highly significant MPH-SODAS treatment effect over ADHD symptoms and over subject functioning in comparison to placebo, according to both SNAP-IV and CGI scores ($p \leq 0.001$ for all analyses). There was no significant sequence or period effect, although we detected a trend for a sequence effect in both inattentive and hyperactivity/impulsivity dimensions of the SNAP-IV scale ($p=0.06$ for both analyses). As expected, baseline SNAP-IV and CGI severity scores were significantly associated with response to treatment ($p \leq 0.001$ for all analyses). There were also significant dose-within-treatment effects - only for CGI Severity and CGI Clinical Improvement scores ($p \leq 0.001$ for both analyses) (see Table 2 and Figure 2).

Insert Table 2 and Figure 2 about here

With regard to the *number of days with drug use*, there was no significant treatment ($p=0.10$), period ($p=0.62$) and order effects ($p = 0.37$), but significant effects for baseline

score [$F(1, 14) = 54211.33$, $p \leq 0.001$] and dose-within-treatment [$F(1, 14) = 3.22$, $p = 0.04$]. When using MPH-SODAS, subjects presented a slight decrease in the number of days with drug use while doses of medication were increased (5.94 days, SD= 2.02 at 0.3 mg/kg/day; 5.87 days, SD = 2.03 at 0.7 mg/kg/day and 5.56 days, SD = 2.03 at 1.2 mg/kg/day). However, while on placebo, there was no change in drug use (6.13 days, SD= 2.29 at 0.3 mg/kg/day; 5.87 days, SD = 2.07 at 0.7 mg/kg/day and 6.0 days, SD = 2.10 at 1.2 mg/kg/day). As for the *number of marijuana cigarettes per day*, there was no significant treatment, period, order, baseline score or dose-within-treatment effects ($p \geq 0.2$ in all analyses). There was also no significant change in the status of *urine tests* for both cannabis and cocaine through the study ($p = 1$ in all analysis). We had no report of MPH misuse.

Medication was well tolerated and we were not able to detect any significant treatment ($p= 0.90$), order ($p=0.51$) and dose-within-treatment ($p=0.90$) effects on SERS total score, although significant period [$F(1, 14) = 7.52$, $p = 0.02$] and baseline scores effects [$F(1, 14) = 115.69$, $p \leq 0.001$] were found. Treatment with MPH-SODAS significantly reduced *appetite* [$F(1, 14) = 15.70$, $p \leq 0.001$], with no period effect ($p=0.38$), but a significant order effect [$F(1, 14) = 5.65$, $p = 0.03$] was found. There were trends to baseline score ($p = 0.06$) and dose-within-treatment ($p=0.07$) effects. No treatment effect was found for insomnia and headache (analyses available upon request).

DISCUSSION

In the present study, MPH-SODAS was significantly superior to placebo in reducing ADHD symptoms and improving global functioning for all main outcome measures (SNAP-

IV and CGI scores). There was no treatment effect over illicit SUD and MPH-SODAS was well-tolerated, despite causing more appetite reduction than placebo.

Our results showing a treatment effect for MPH on ADHD symptoms in adolescents with illicit SUD are in contrast with some RCTs with stimulants in adults[19-21]. A combination of factors, such as MPH dosage, type of MPH delivery system, type of abused drug, and brain development stage might explain these contradictory findings. In our study, for example, we administered higher MPH doses than those utilized in the study by Carpentier et al[19]. Besides, our sample was comprised mostly of marijuana plus cocaine users, in contrast to cocaine[19, 20] and cocaine/heroin[21] users in adults´ protocols. Moreover, neurobiological differences among adults and adolescents may influence MPH response. It is well-established that SUD progression affects the reward system (RS)[38]. Since MPH acts on RS[39], the length of time of drug use might affect brain response to MPH. Also, animal studies documented different brain and behavioral responses to cocaine among adolescent vs. adult rats[24, 25]. Lastly, the adolescent brain is still in development[40], which might favor recruitment of some brain pathways enrolled in MPH effects. In this sense, our data are in agreement with the only adolescent RCT available, which reported treatment effect over ADHD symptoms with pemoline[17].

There was no significant treatment effect over drug use. Even though some studies showed that ADHD severity might worsen SUD prognosis[10, 11] it is possible to speculate that ADHD improvement in a short period of time (3 weeks) is not enough to decrease drug use in adolescents with chronic use. In this sense, Riggs et al[17] found no drug use improvement as well, despite ADHD improvement. However, Solhkhah et al[16] reported a decrease in drug use in 14 adolescents (6-month bupropion open trial), concomitant with a drug use intervention. It is important to highlight that our protocol lasted for a shorter period of time, and we had no specific intervention for SUD. Even so, we detected a similar pattern of drug use during the

protocol for MPH-SODAS and placebo (no increase in drug use for both groups). Further RCTs with longer periods, incorporating combined SUD intervention and adjusting results for age of onset of SUD, will help clarify the impact of ADHD treatment in SUD. Regarding MPH-SODAS tolerability, we had no serious adverse event.

Our study should be understood in the context of some limitations. First, it was a single-blind protocol. Second, SNAP-IV inattentive and hyperactivity/impulsivity scores had a trend to a sequence effect (p=0.06). Pharmacological properties of MPH (short period of time required to produce clinical significant effects) might facilitate such pattern in a crossover study. Thus, youths who started on MPH-SODAS were less prone to placebo effects than participants who started on placebo (group B), since the formers might quickly recognize effects of stimulants in their ADHD symptoms, being more prone to detected lower clinical response when switched to placebo. Also, we had a small sample size, limiting the power for some analyses (e.g., assessment of interactions) and findings can not be generalized to adolescents with a different pattern of drug use. Furthermore, our trial lasted for 6 weeks, what might not be enough time to appreciate improvement (decrease) in drug use. Also, the presence of other psychiatric comorbidities in the sample (Table 1) might have some impact on treatment effects, although the comorbidity profile was not different between groups. Despite these caveats, our study has some specific strengths: this was the first study to evaluate stimulant effect in a non abstinent outpatient sample of adolescents with ADHD/SUD in a placebo-controlled trial enrolling only treatment naive subjects. Moreover, the sample was comprised mostly by marijuana users and we had a high retention rate (87%).

To the best of our knowledge, this is the first study suggesting effectiveness of stimulants on ADHD symptoms in adolescents with ADHD/SUD. However, randomized clinical trials with larger samples, drug treatment intervention and longer follow-ups, are recommended.

REFERENCES

1. Bukstein OG, Bernet W, Arnold V, Beitchman J, Shaw J, Benson RS et al.: Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. J Am Acad Child Adolesc Psychiatry 2005; 44:609-21.

2. Galduroz JC, Noto AR, Nappo SA, Carlini EA: Household survey on drug abuse in Brazil: study involving the 107 major cities of the country--2001. Addict Behav 2005; 30:545-56.

3. World Health Organization (WHO): available at http://www.who.int/substance_abuse/facts/cannabis/en/index.html (assessed January 08, 2006).

4. Polanczyk G, Horta B, Lima M, Biederman J, Rohde LA. The worldwide prevalence of ADHD. A systematic review and meta-regression analysis. Am J Psychiatry (*in press*).

5. Rohde LA, Biederman J, Busnello EA, Zimmermann H, Schmitz M: ADHD in a school sample of Brazilian adolescents: a study of prevalence, comorbid conditions and impairments. J Am Acad Child Adolesc Psychiatry 1999; 38:716-722.

6. Rohde LA. ADHD in Brazil: the DSM-IV criteria in a culturally different population. J Am Acad Child Adolesc Psychiatry. 2002 Sep;41(9):1131-3.

7. Lesesne C, Abramowitz A, Perou R, Brann E: Attention deficit/hyperactivity disorder: A public health research agenda. http://www.cdc.gov/ncbddd/adhd/ dadphra.htm. 2000. Accessed on 08/01/2006.

8. Horner BR, Scheibe KE. Prevalence and implications of attention-deficit hyperactivity disorder among adolescents in treatment for substance abuse. J Am Acad Child Adolesc Psychiatry. 1997; 36(1):30-6.

9. Kuperman S, Schlosser SS, Kramer JR, Bucholz K, Hesselbrock V, Reich T, Reich W. Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. Am J Psychiatry. 2001; 158(12):2022-6.

10. Ercan ES, Coskunol H, Varan A, Toksoz K. Childhood attention deficit/hyperactivity disorder and alcohol dependence: a 1-year follow-up. Alcohol Alcohol. 2003; 38(4):352-6.

11. White AM, Jordan JD, Schroeder KM, Acheson SK, Georgi BD, Sauls G, Ellington RR, Swartzwelder HS. Predictors of relapse during treatment and treatment completion among marijuana-dependent adolescents in an intensive outpatient substance abuse program. Subst Abus. 2004; 25(1):53-9.

12. Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M; Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45(6):642-57

13. Volkow ND, Fowler JS, Wang GJ: The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology 2004; 47 3-13.

14. Volkow ND, Wang GJ, Fowler JS, Ding YS. Imaging the effects of methylphenidate on brain dopamine: new model on its therapeutic actions for attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57(11):1410-5.

15. Riggs PD, Leon SL, Mikulich SK, Pottle LC. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry. 1998; 37(12):1271-8.

16. Solhkhah R, Wilens TE, Daly J, Prince JB, Van Patten SL, Biederman J. Bupropion SR for the treatment of substance-abusing outpatient adolescents with attention-deficit/hyperactivity disorder and mood disorders. J Child Adolesc Psychopharmacol. 2005; 15(5):777-86.

17. Riggs PD, Hall SK, Mikulich-Gilbertson SK, Lohman M, Kayser A. A randomized controlled trial of pemoline for attention-deficit/hyperactivity disorder in substance-abusing adolescents. J Am Acad Child Adolesc Psychiatry. 2004; 43(4):420-9.

18. Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, Lockhart N, Edwards A, Donlin J, Pihlgren E. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Exp Clin Psychopharmacol. 2002; 10(3):286-94.

19. Carpentier PJ, de Jong CA, Dijkstra BA, Verbrugge CA, Krabbe PF. A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. Addiction. 2005; 100(12):1868-74.

20. Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: Double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend. 2007; 87(1):20-9.

21. Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug Alcohol Depend. 2006; 81(2):137-48.

22. Kuperman S, Perry PJ, Gaffney GR, Lund BC, Bever-Stille KA, Arndt S, Holman TL, Moser DJ, Paulsen JS. Bupropion SR vs. methylphenidate vs. placebo for attention deficit hyperactivity disorder in adults. Ann Clin Psychiatry. 2001; 13(3):129-34.

23. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry 2003; 160(6):1041-52.

24. Stansfield KH, Kirstein CL. Neurochemical effects of cocaine in adolescence compared to adulthood. Brain Res Dev Brain Res. 2005;159(2):119-25.

25. Badanich KA, Adler KJ, Kirstein CL. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. Eur J Pharmacol. 2006;550(1-3):95-106.

26. Liu F, Muniz R, Minami H, Silva RR. Review and comparison of the long acting methylphenidate preparations. Psychiatr Q. 2005;76(3):259-69.

27. Rohde LA, Szobot C, Polanczyk G, Schmitz M, Martins S, Tramontina S. Attention-deficit/hyperactivity disorder in a diverse culture: do research and clinical findings support the notion of a cultural construct for the disorder? Biol Psychiatry. 2005 Jun 1;57(11):1436-41.

28. Amorim P: Mini International Neuropsychiatric Interview (MINI): Validação de entrevista breve para diagnóstico de transtornos mentais. Revista Bras Psiquiatr 2000; 22:106-115.

29. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S: A children's global assessment scale (CGAS). Arch Gen Psychiatry 1983; 40:1228-31.

30. Associação Brasileira de Empresas de Pesquisas. Critério de Classificação Econômica Brasil: available at http://www.anep.org.br/codigosguias/CCEP.pdf (assessed April 18, 2005).

31. Wechsler D: WISC-III/Manual. New York, NY: The Psychological Corporation. 1991.

32. Wechsler D: Manual of the Wechsler Adult Intelligence Scale (3rd edition). San Antonio TX: The Psychological Corporation. 1997.

33. Swanson J. 1992. School-Based Assessments and Interventions for ADD Students. Irvine, CA: KC Publishing.

34. National Institute of Mental Health. CGI (Clinical Global Impression) scale. Psychopharmacol Bull 1985; 21:839-843.

35. Barkley RA. 1990. Attention deficit Hyperactivity disorder: A handbook for diagnosis and treatment. New York: Guilford Press.

36. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen Psychiatry. 2004; 61(3):310-7.

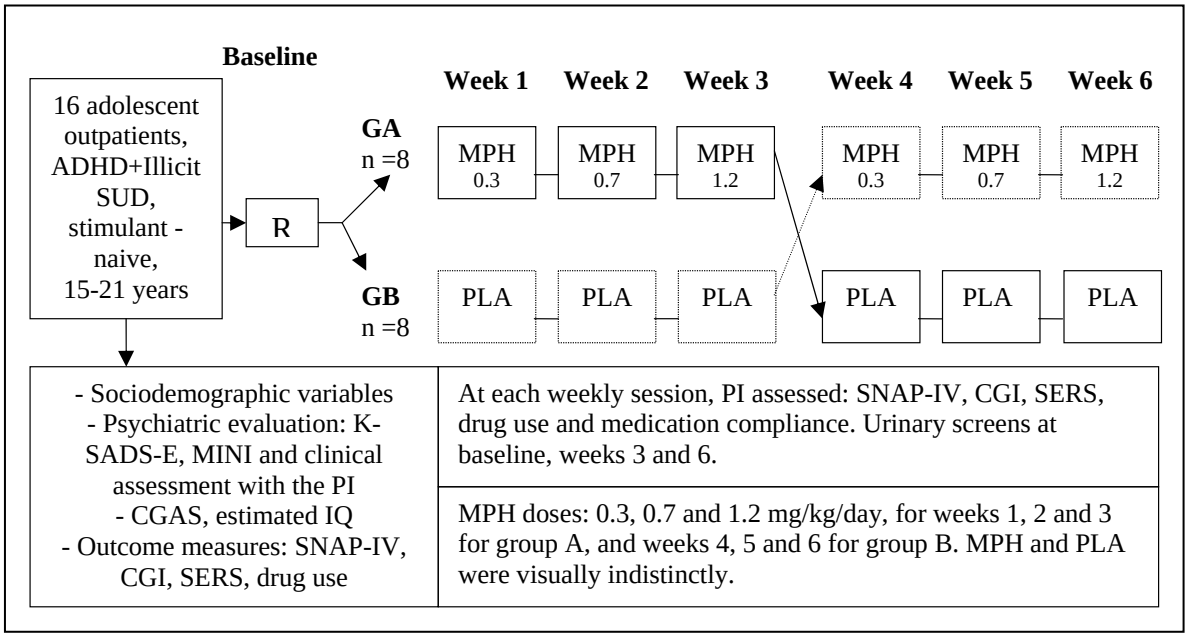
37. Littell RC, Pendergast J, Natarajan R. Modelling covariance structure in the analysis of repeated measures data, Stat Med. 2000;19(13):1793-819.

38. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997; 278(5335):52-8.

39. Volkow ND, Wang GJ, Fowler JS, Telang F, Maynard L, Logan J, Gatley SJ, Pappas N, Wong C, Vaska P, Zhu W, Swanson JM. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. Am J Psychiatry. 2004; 161(7):1173-80.

40. Toga AW, Thompson PM, Sowell ER. Mapping brain maturation. Trends Neurosci. 2006; 29(3):148-59.

Figure 2 (1) – Flow chart of study design and procedures



Note: *ADHD* = Attention Deficit/ Hyperactivity Disorder; *SUD* = Substance Use Disorder; *R* = randomization; *GA* = Group A; *GB* = Group B; *K-SADS-E* = Schedule for Affective Disorders and Schizophrenia for School – Age Children, Epidemiological Version; *MINI* = Mini International Neuropsychiatry Interview; *PI* = principal investigator; *CGAS* = Clinical Global Assessment Scale; *IQ* = Intelligence quotient; *SNAP-IV* = Swanson, Nolan and Pelham Scale – version IV; *CGI* = Clinical Global Impression Scale; *SERS* = Barkley Side Effect Rating Scale; *MPH* = methylphenidate SODAS; *PLA* = Placebo.

Table 6 (1) - Sociodemographic and clinical characteristics of the participants according to study randomization

Characteristic	Sample (n=16)				P Value
	Group A (n=8)		Group B (n=8)		
	mean (SD)	% (N)	mean (SD)	% (N)	
Age (in years):	17.50 (2.33)		17.38 (2.2)		0.91
Ethnicity: (European-Brazilian):		37.5 (3)		87.5 (7)	0.06
Socioeconomic level: A + B+ C		50.0 (4)		87.5 (7)	0.14
D + E		50.0 (4)		12.5 (1)	
Divorced parents:		37.5 (3)		50.0 (4)	0.50
School (mean grade):	7.13 (2.23)		7.75 (1.67)		0.54
Estimated IQ:	79.43 (16.66)		84.75 (21.16)		0.60
SNAP-IV: Total score	50.38 (18.05)		50.38 (8.93)		0.95
Inattentive score	18.13 (7.26)		18.63 (5.50)		0.88
Hyperactive score	18.75 (7.38)		19.25 (5.26)		0.88
ODD score	13.38 (6.63)		13.0 (5.40)		0.90
Further lifetime DSM-IV Axis Diagnosis:					
Conduct Disorder		100 (8)		75(6)	0.47
Oppositional Defiant Disorder		25(2)		37.5(3)	1.00
Depression		12.5(1)		25(2)	1.00
CGI-severity	5.88 (0.84)		5.50 (0.55)		0.30
Clinical Global Assessment Scale:	44.38 (12.08)		40.0 (4.63)		0.36
SUD: Marijuana		100.0 (8)		87.5 (7)	0.50
Cocaine		50.0 (4)		37.5 (3)	0.50
Days of cannabis use, last month	30 (0.0)		28.57 (3.78)		0.30
Number of cannabis cigarettes per day	3 (0.76)		2.71 (0.95)		0.54

Note: *ADHD* = Attention Deficit/ Hyperactivity Disorder; *SNAP-IV* = Swanson, Nolan and Pelham Scale – version IV; *CGI* = Clinical Global Impression Scale; *SUD* = Substance Use Disorder; *IQ* = Intelligence quotient; *MPH* = methylphenidate SODAS; *PLA* = Placebo. *Group A:* MPH-SODAS on weeks 1, 2, 3 and PLA on weeks 4, 5, 6. *Group B:* PLA on weeks 1, 2, 3 MPH-SODAS on weeks 4, 5, 6.

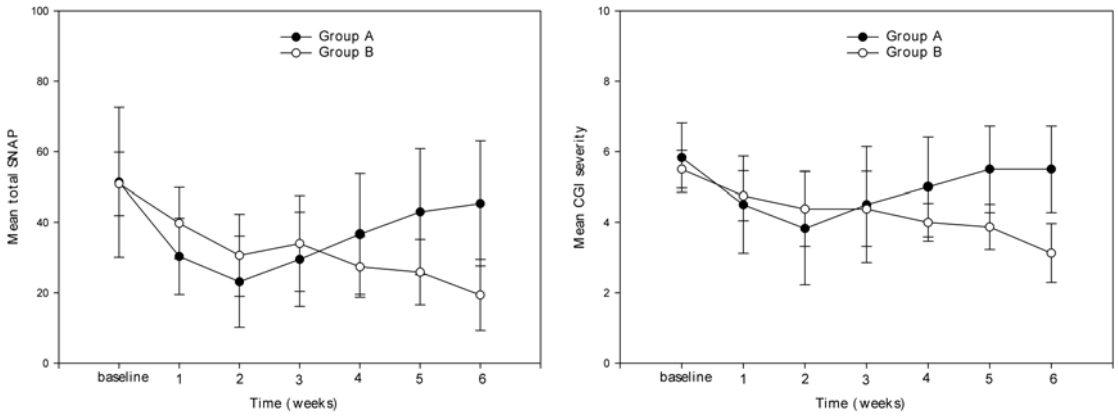
.

Table 7 (2) - Mixed Effect Model Analyses for effects of MPH-SODAS vs. Placebo on SNAP-IV and CGI scores in adolescents with both ADHD and illicit SUD (n=16)

	Treatment	Period	Sequence	Dose-within-treatment
SNAP Total[a]	$F(1, 14) = 42.92$ ***p* value ≤ 0.001**	$F(1, 14) = 20.77$ *p* value = 0.33	$F(1, 14) = 16.08$ *p* value = 0.11	$F(1, 14) = 29.57$ *p* value = 0.16
SNAP Inattentive[b]	$F(1, 14) = 14.31$ ***p* value = 0.001**	$F(1, 14) = 12.40$ *p* value = 0.99	$F(1, 14) = 12.43$ *p* value = 0.06	$F(1, 14) = 11.41$ *p* value = 0.34
SNAP Hyperactivity[c]	$F(1, 14) = 28.75$ ***p* value ≤ 0.001**	$F(1, 14) = 23.02$ *p* value = 0.77	$F(1, 14) = 13.35$ *p* value = 0.06	$F(1, 14) = 59.80$ *p* value = 0.64
CGI Severity[b]	$F(1, 14) = 13.67$ ***p* value ≤ 0.001**	$F(1, 14) = 13.54$ *p* value = 0.51	$F(1, 14) = 13.91$ *p* value = 0.19	$F(1, 14) = 13.55$ ***p* value = 0.001**
CGI Clinical improvement[d]	$F(1, 14) = 25.31$ ***p* value ≤ 0.001**	$F(1, 14) = 18.97$ *p* value = 0.6	$F(1, 14) = 21.33$ *p* value = 0.26	$F(1, 14) = 32.28$ ***p* value ≤ 0.001**
CGI Efficacy[e]	$F(1, 14) = 72.58$ ***p* value ≤ 0.001**	$F(1, 14) = 72.58$ *p* value = 0.65	$F(1, 14) = 14.11$ *p* value = 0.21	$F(1, 14) = 71.21$ *p* value = 0.24

Note: Significant values are highlighted in bold. Best Covariance Structure: [a]Toeplitz; [b]Unstructured [c]ARMA(1,1); [d]First-Order-Ante-Dependence; [e]Compound Symmetry. *MPH-SODAS* = methylphenidate SODAS; *ADHD* = Attention Deficit/ Hyperactivity Disorder; *SUD* = Substance Use Disorder; *SNAP-IV* = Swanson, Nolan and Pelham Scale – IV revision; *CGI* = Clinical Global Impression Scale.

Figure 3 (2) - SNAP-IV and CGI-Severity mean scores during the protocol for MPH-SODAS and Placebo groups in adolescents with ADHD and SUD (n=16)



Note: *ADHD* = Attention Deficit/ Hyperactivity Disorder; *SNAP-IV* = Swanson, Nolan and Pelham Scale – version IV; *CGI* = Clinical Global Impression Scale; *SUD* = Substance Use Disorder; *MPH* = methylphenidate SODAS; *PLA* = Placebo. *Group A:* MPH-SODAS on weeks 1, 2, 3 and PLA on weeks 4, 5, 6. *Group B:* PLA on weeks 1, 2, 3 MPH-SODAS on weeks 4, 5, 6.

7 ESTUDO 3 - QUESTÃO DE PESQUISA

Como é a ligação do metilfenidato ao transportador de dopamina, em adolescentes com TDAH e TUSP?

ARTIGO PRINCIPAL 3

Methylphenidate DAT binding in adolescents with Attention-Deficit/ Hyperactivity Disorder comorbid with Substance Use Disorder - a single Photon Emission Computed Tomography with [Tc^{99m}]TRODAT-1 study

In press, Neuroimage

Methylphenidate DAT binding in adolescents with Attention-Deficit/ Hyperactivity Disorder comorbid with Substance Use Disorder - a single Photon Emission Computed Tomography with [Tc^{99m}]TRODAT-1 study

Claudia M. Szobot[1, 2, 3], Ming Chi Shih[4], Thais Schaefer[3], Neivo Júnior[5], Marcelo Q. Hoexter[4], Ying Kai Fu[6], Flávio Pechansky[2], Rodrigo A. Bressan[4], Luis A. P. Rohde[1]

[1]ADHD Outpatient Clinic, Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul (UFRGS). Porto Alegre (POA), Estado do Rio Grande do Sul (RS), Brasil. [2]Center for Drug and Alcohol Research, HCPA, UFRGS, POA, Brazil. [3]Universidade Luterana do Brasil, Curso de Medicina. Canoas, RS, Brazil. [4]Laboratório Interdisciplinar de Neurociências Clínicas (LINC), Universidade Federal de São Paulo (UFSP), São Paulo, Brasil. [5]Irmandade Santa Casa de Misericórdia, POA, RS, Brasil; [6]Institute of Nuclear Energy Research (INER), Long-Tan, Taiwan, Republic of China.

Corresponding author: Claudia M. Szobot. Programa de Déficit de Atenção/ Hiperatividade, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul. Address: Rua Ramiro Barcelos, 2350. CEP: 90035-003. Porto Alegre, RS, Brasil. Phone/fax: 55-51-3330-5813. **e-mail:** cmszobot@terra.com.br

Words in the abstract: 219

Words in the text: 3.145

Figures: 1

Tables: 2

ABSTRACT

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is highly prevalent among adolescents with Substance Use Disorders (SUD). Effects of methylphenidate (MPH) on ADHD are attributed to its properties of blocking the dopamine transporter (DAT) in the striatum. However, it has been demonstrated that drug addiction is associated with dopaminergic system changes that may affect MPH brain effects, emphasizing the need to better understand MPH actions in subjects with ADHD+SUD. **Objectives:** To evaluate the effect of an extended release formulation of MPH (MPH-SODAS) on DAT density in 17 stimulant-naive adolescents with ADHD+SUD (cannabis and cocaine). **Methods:** Subjects underwent two single photon emission computed tomography (SPECT) scans with [Tc^{99m}]TRODAT-1, at baseline and after 3 weeks on MPH-SODAS. Clinical assessment for ADHD relied on the Swanson, Nolan and Pelham Scale – version IV (SNAP-IV). Caudate and putamen DAT binding potential (BP) was calculated. **Results:** After 3 weeks on MPH-SODAS, there was a significant reduction of SNAP-IV total scores ($p < 0.001$), and significant reductions of DAT BP at the left and right caudate. Similar decreases were found at the left and right putamen ($p<0.001$ for all analyses). **Discussion**: This study shows that the magnitude of DAT blockade induced by MPH in this population is similar to what is found in ADHD patients without SUD comorbidity, providing neurobiological support for trials with stimulants in adolescents with ADHD+SUD.

Key-words: Attention-Deficit/Hyperactivity Disorder, Substance Use Disorders, methylphenidate, SPECT, dopamine transporter, adolescents.

INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is a prevalent disorder worldwide, as recently documented by our group (Polanczyk et al., 2007). The disorder is characterized by excessive childhood onset inattention, hyperactivity and impulsivity (American Psychiatric Association, 1994), tending to persist into adulthood. Affected subjects usually present with one or more comorbidities (Spencer et al., 2007). Individuals with ADHD are at higher risk for further Substance Use Disorder (SUD) (Molina et al., 1999; Biederman et al., 2006; Szobot et al., 2007) and a high ADHD prevalence is found in samples of adolescents with SUD (DeMillio, 1898; Kupermann et al., 2001; Horner and Scheibe, 1997). Moreover, ADHD affects SUD prognosis, being associated with both earlier and more frequent alcohol relapses (Ercan et al., 2003) and lower likelihood of cannabis treatment completion in adolescents (White et al., 2004).

Several evidence-based guidelines suggest that stimulants are first line treatment for ADHD (Pliszka et al., 2006), but up to now little is known about clinical and brain effects of methylphenidate (MPH) in adolescents with ADHD+SUD. Interestingly, although more than a hundred controlled trials have evaluated MPH effects in ADHD samples, the vast majority of these studies did not include subjects with use/misuse/abuse or dependence of alcohol or illicit drugs. Since both MPH (Spencer et al., 2006) and most abused drugs (Volkow et al., 2004; Rodriguez de Fonsenca et al., 2005; Koob, 2006; Tzavara et al., 2006) have a clear impact on the dopaminergic system, MPH clinical and neurobiological effects documented in non-SUD samples might not necessarily be generalized to this dually-diagnosed population. Still few pharmacological trials evaluated MPH effects on subjects with ADHD+SUD. Some

studies with adults did not find a superior effect of MPH over placebo (Carpentier et al., 2005; Levin et al., 2007) or over placebo and bupropion (Levin et al., 2006). Up to now, to the best of our knowledge, just one study evaluated MPH effects on adolescents with ADHD+SUD, suggesting a significant MPH treatment effect (Szobot et al., *submitted*).

In addition, little is known about the MPH brain effects of blocking DAT in individuals with ADHD+SUD. Brain imaging studies in ADHD strongly support the involvement of fronto-striatal-cerebellar circuits (Krain and Castellanos, 2006), where dopamine (DA) plays an important function. In vivo molecular imaging studies with positron emission tomography (PET) and single photon emission computed tomography (SPECT) have shown a higher striatal dopamine transporter (DAT) density in subjects with ADHD, ranging from 70% (Doughherty et al., 1999) to 5% (Larisch et al., 2006) increases in DAT density. Concerning MPH mechanism of action, two studies have shown that this drug induces significant decrease in [^{11}C]raclopride binding at the D_2 receptor, presumably due to increased synaptic DA levels which is believed to mediate the therapeutic effects of MPH (Schlaepfer et al., 1997; Volkow et al., 1995). Moreover, Dresel (2000) found that specific binding of [Tc^{99m}]TRODAT-1 to DAT decreased significantly in adults with ADHD after MPH treatment. Other studies found similar results (la Fougere et al., 2006; Krause et al., 2005).

The generalization of these results to samples of individuals with ADHD+SUD might have limitations, since these investigations did not include subjects with drug use, similarly of what is seen in clinical studies. Although some dysfunctions in the dopaminergic system of drug addicted patients have been well characterized, such as decreased D2 receptors and DAT (Volkow et al., 2004; Volkow et al., 1995), it is still not clear what the effects of these changes in patients with an additional ADHD diagnosis are. Most abused drugs interfere in fronto-striatal-cerebelum circuits (Koob, 2006; Tzavara et al., 2006). Cocaine, for example,

increases DA by blocking striatal DAT (Volkow et al., 1995), the same target of MPH. Moreover, there is a body of evidence describing that cannabis, the most abused drug worldwide (World Health Organization, 2006), affects dopamine regulation (Price et al., 2007).

Given that the presence of acute or chronic drug use might result in striatal dopaminergic changes, it is important to elucidate if the MPH mechanism of action is preserved under these circumstances. Thus, the goal of the present study was to evaluate the effect of ADHD treatment with a extended release formulation of methylphenidate (MPH-SODAS) on striatal DAT density in a treatment-naive sample of adolescents with ADHD+SUD (cannabis and cocaine) using [Tc^{99m}]TRODAT-1 and SPECT before and after the intervention.

METHODS

Study design and participants

This was a 3-week study on the effects of MPH-SODAS on DAT density assessed by SPECT with [Tc^{99m}]TRODAT-1 in 17 outpatient male adolescents with both ADHD/SUD. All subjects underwent 2 brain scans: one at baseline and another after 3 weeks on escalated doses of MPH-SODAS. The study was conducted in the city of Porto Alegre (capital of Brazilian Southernmost State, Rio Grande do Sul). The project was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre (approved as an IRB by

the Office for Human Research Protections, United States of America - IRB 00000921). Written informed consent was obtained from all participants and their parents.

Subjects were recruited from a previous study assessing ADHD in a large community sample of adolescents with SUD (6) (n=14) and by advertisements in local newspapers and radio broadcasts (n=3). Inclusion criteria were: a) age range between 15 and 21 years-old; b) male gender; c) current DSM-IV diagnosis of abuse / dependence of marijuana or cocaine; d) current DSM-IV diagnosis of ADHD; e) stimulant-naive subjects. Exclusion criteria included: a) lack of a responsible adult to inform about possible childhood psychopathology or to take responsibility for the medication; b) need for inpatient treatment for drug abuse or psychiatric comorbidities; c) presence of a primary psychiatric condition that required immediate outpatient treatment (like moderate/severe depression); d) inhalant use.

Study medication procedures

Medication was taken once a day (in the morning), by oral administration. Study compliance was assessed by self-report, mother's report and pill counting. Subjects received 0.3 mg/kg/day of MPH-SODAS at week 1, 0.7 mg/kg/day at week 2 and 1.2 mg/kg/day at week 3. On the day of the second scan, all subjects received the medication by a staff member at the moment of [Tc^{99m}]TRODAT-1 injection, thus ensuring that all subjects had the same time interval between MPH-SODAS intake and brain imaging acquisition (4hs).

Each MPH-SODAS capsule contains a 50:50 mixture of immediate release (IR) and enteric-coated delayed release (EC-DR) beads, resulting in a bimodal release pattern which is equivalent to twice daily immediate-release MPH. The IR beads yield an initial peak at about 2 hours and the EC-DR beads yield a second peak on average at 6.5 hours (Liu et al, 2005).

Diagnostic Procedures

The diagnoses of ADHD and comorbid mental disorders were confirmed by semi – structured interviews (Portuguese version of the *Schedule for Affective Disorders and Schizophrenia for School – Age Children, Epidemiological Version – K-SADS-E)* (Mercadante et al., 1995) with the parents, and clinical interviews with the adolescent and the parents conducted by a child psychiatrist (CMS). Detailed description of the diagnostic process in our ADHD clinic can be found elsewhere (Rohde et al., 2005). The diagnoses of SUD relied on the drug section of the *Mini International Neuropsychiatry Interview* (MINI), Brazilian version, which generates diagnoses of abuse or dependence according to DSM-IV criteria (Amorim, 2000). Participants had drug use confirmed by urinary tests (cannabis and/or cocaine), at baseline and after 3 weeks. Other measures included: a) the *Brazilian Association of Market Research Form* for socioeconomic status evaluation (SES) (Associação Brasileira de Empresas de Pesquisas, 2005); b) Block Design and Vocabulary subtests of the *Wechsler Intelligence Scal*e – 3rd edition (WISC-III) and the *Wechsler Adult Intelligence Scal*e (WAIS) for estimation of IQ (Wechsler, 1991 and Wechsler 1997); c) the *Clinical Global Assessment Scale* (CGAS) (Shaffer et al., 1983); d) the *Swanson, Nolan and Pelham Scale – version IV (SNAP-IV),* which is a 26-item scale, based on DSM-IV ADHD and Oppositional Defiant Disorder (ODD) symptoms, for ADHD severity (Swanson et al., 2001). Items are scored on a 4-point scale (from 0, *never*, to 3, *very often*). The instrument has its Portuguese version already assessed (Mattos et al., 2006). In the present study, the SNAP-IV evaluation was based on the mother's report. Sociodemographic information was systematically collected.

DAT Imaging Acquisitions

SPECT scans were performed with [Tc99m]-TRODAT-1, a radiotracer with high selectivity and specificity for the DAT. TRODAT-1 kits were produced by the Institute of Nuclear Energy Research (INER-Taiwan R.O.C.) and labeled according to Choi (1999). Images were acquired four hours after the injection of 740 MBq (±74) of [Tc99m]-TRODAT-1 using a Dual-head gamma camera "ECAM" (Siemens Medical System, USA), fitted with low-energy, general purpose, fanbeam-hole collimators. For each scan a total of 128 projections (30 s per frame) were collected in a step-and-shoot mode on circular orbit with the mean radius of rotation of 15cm.

The image data were reconstructed by standard filtered backprojection using a Butterworth filter (cut-off frequency 0.35 Nq) and attenuation was corrected using Chang's first-order method (attenuation coefficient m ¼ 0.12 cm_1).

Image data analysis

All the SPECT images are converted from dicom to analyze file through MRIcro Program (www.mricro.com) and transfer to nifti file by Stastistic Paramentric Mapping 5 program (SPM5) mounted in MATLAB 7.0 plataform. Reorietation was corrected for all SPECT imaging and spacially normalized to a standardized image space based on a select subject image, after the four time repeat process, creating the specific template image for the study. Spatial normalization is performed by linear and non linear transformation algorithm with parameters consistent and the imaging data was then applied to match each image to the template provided from all imaging data study. The imaging data was also smoothed with an

isotropic Gaussian filter to improve the signal-to-noise ratio and to reduce errors attributed to individual variation in striatum anatomy. Resulting transformations was post-processed to generate maps of the deformation at each voxel during the normalization process.

Volumetric regions of interest (vROIs) in striatum (caudate and putamen) and occipital lobe are manually delineated by radiologist and nuclear medicine physician using neuroanatomy atlas (www.sph.sc.edu/comd/rorden/anatomy/home.html) onto the template using SPM5 Volume toolbox. DAT density was calculated with binding potential (BP) using vROIs bilaterally drawn in the striatum (STR) separately as: caudate and putamen and in the occipital cortex (OCC) as background. BP was calculated by the following formula: [(STR–OCC)/OCC].

Data analyses

Student's paired *t* tests were used to compare the average differences in [Tc^{99m}]TRODAT-1 binding in the left and right caudate and putamen before and after 3 weeks on MPH-SODAS. The same procedures were used to evaluate average changes in ADHD symptoms (SNAP-IV) and drug use (subject's report). Pearson correlation was used to test the association between MPH dosage and DAT occupancy. Linear logistic regression was used to test whether the final total score at SNAP-IV could be predicted by baseline or Δ (baseline – 3-week) TRODAT-binding, adjusting results for baseline total SNAP-IV score and drug use. For TRODAT-1 binding analyses, we tested separately both left and right caudate and putamen. A significance level of 5% was set for all analyses.

RESULTS

The sample was comprised by 17 male adolescents with both ADHD and illicit SUD. All participants had a cannabis SUD diagnosis, smoking approximately 3 marijuana cigarettes/day. However, 5 subjects reported cocaine as the main drug (4 crack, 1 snorted cocaine). In addiction, 4 subjects had an Alcohol Use Disorder (AUD) and 16 smoked nicotine everyday. It is important to note that we tested correlations between nicotine and baseline DAT levels at putamen and caudate, considering both the amount of nicotine cigarettes smoked on daily basis and the amount of nicotine smoked between the injection of TRODAT-1 and image acquisitions. All tested correlations were not significant (all P values ≥ 0.37). None of the subjects was under SUD treatment. All adolescents fulfilled DSM-IV ADHD diagnostic criteria before the age of 5 years and the ADHD most common type was the combined (n=12; 70.58%), followed by the inattentive (n=3; 17.64%) and the hyperactive (n=2; 11.76%) types. No individual had ever received ADHD treatment. Subjects demographic, clinic characteristics and mean IQ are described in Table 1.

Please insert Table 1 about here

After 3 weeks on MPH-SODAS, subjects had a significant reduction in striatal TRODAT-1 binding (both left and right caudate and putamen), concomitant to a significant decrease in ADHD symptoms and reported drug use, as shown in Table 2 ($p<0.005$ in all analysis). Since changes in acute nicotine use could be a confounder (Krause et al., 2002), we assessed the number of nicotine cigarettes smoked in the time interval between TRODAT-1 injection and brain scan on both baseline and after 3 weeks on MPH-SODAS conditions. No significant difference was found between baseline and Time 1 (mean number of nicotine

cigarettes at baseline SPECT: 1.4, SD=1.06; after 3 weeks: 1.6, SD= 1.35; p=0.60). Although subject's reported a reduction in the number of days with drug use (see Table 2), the only changes we had in the urinary tests were one exam turning negative for cocaine (remaining positive for cannabis) and another turning positive for cocaine (was negative for both cocaine and cannabis at baseline). In Figure 1 we show a brain scan of a subject before and after medication, illustrating the significant TRODAT-1 binding reduction observed in the sample. It's is important to note that our results did not change when analyzing separately individuals with and without cocaine use (data available under request).

Please insert Table 2 and Figure 1 about here

Although at week 3 all subjects received the same MPH dosage according to a body weight criteria (1.2 mg/kg/day), some subjects received 60mg (n=11) and others 80mg (n=6) of MPH. In this sense, we found significant correlations between MPH absolute dosage (60 or 80 mg) and Δ TRODAT-1 binding at left caudate (r = 0.543, P= 0.05), right caudate (r= 0.511, P =0.05) and right putamen (r= 0.517, P=0.05). Interestingly, there was no significant correlation between different absolute dosage and clinical improvement according to SNAP-IV scale (data available under request).

We additionally tested whether baseline or Δ TRODAT-1 binding in each ROI assessed could predict clinical improvement according to total SNAP-IV scores at the 3rd week of treatment, adjusting results for baseline SNAP-IV scores and changes in drugs use. No significant result emerged for total SNAP-IV score ($p > 0.12$ for all analyses).

DISCUSSION

In the present study, a 3-week treatment with MPH-SODAS significantly reduced striatal DAT density, concomitantly to an improvement in ADHD symptoms and a reduction in reported drug use. In addition, there was a significant correlation between total daily MPH dosage (60 vs 80 mg) and DAT density. To the best of our knowledge, this is this first study documenting MPH cerebral effects in a clinical sample of adolescents with ADHD + SUD.

Our results showing an association between MPH-SODAS treatment and a decrease in striatal DAT binding is in agreement with a previous study with [Tc^{99m}]TRODAT-1 in a sample of adults with ADHD (Krause et al., 2000). In this study, authors reported a significant reduction in striatal DAT binding after 4 weeks on MPH use. However, this study did not include subjects with SUD. The comparison between our data and those from other studies might face some methodological challenges, such as: a) the presence of a SUD diagnosis – while our study necessarily requested current drug use as an inclusion criteria, other studies excluded individuals with drug use (la Fougere et al., 2006; Krause et al., 2005; Krause et al., 2005). This is a key issue, since some typical drug effects, such as high and reinforcing, are related to an increasing in DA level in brain areas including striatum (Koob, 2006). Cocaine use, for example, might be associated to more prolonged changes in DAT regulation, such as changes in DAT surface expression (Cowel et al., 2000; Daws et al., 2002). Cannabis, the most used drug in our sample, also affects dopaminergic circuits. The highest density of CB1 receptors has been demonstrated to locate in basal ganglia and cerebellum (Herkenham et al., 1990). There is a body of evidence showing that stimulation of CB1 receptors is associated to dopamine increase levels at basal ganglia, and also that cannabinoid agonists might additionally inhibit DAT activity via other targets than CB1, corroborating the idea of a

multilevel interaction between endocannabinoids and dopamine regulation (Rodriguez de Fonseca et al., 2005; Tzavara et al., 2006; Price et al., 2007). Age range: our study evaluated adolescents. This might have implications, since it is well-established that SUD progression affects the reward system (RS) (Koob and Moal, 1997; Volkow et al., 2005). Since MPH acts on RS (Spencer et al., 2006; Volkow et al., 1995), it seems logical to speculate that the length of time of drug use might affect brain response to MPH. Also, animal studies have documented different brain and behavioral responses to cocaine among adolescent vs. adult rats (Stansfield and Kirstein, 2005; Badanich et al., 2006). c) Medication regime: while our study lasted for 3 weeks, others lasted longer (Krause et al., 2005). Also, studies vary according to type of MPH formulation (for instance, MPH-SODAS vs. MPH-IR).

We also had a significant correlation between MPH dosage and DAT occupation. That is, higher MPH dosages (80mg/day) were associated to lower TRODAT binding (more MPH binding at DAT). Similar tendency was already described, but not with drug addicts. A PET study using [^{11}C]cocaine have estimated the DAT occupancy of different doses of MPH in 7 healthy volunteers and found a dose-dependent DAT occupancy, with mean values of 12% (5mg), 40% (10mg), 54% (20mg), 72% (40mg), and 74% (60mg) 2hs after administration of the drug (Volkow et al., 1998). The estimated MPH dose required to block half of the DAT was 0.25mg/kg of oral MPH blockade of DAT at the striatum (Spencer et al., 2006; Volkow et al., 1995).

In our investigation, DAT binding in caudate and putamen did not predict response to MPH. Although Error Type II in this small sample might be the most appealing explanation for this lack of association, it is important to note that contradictory findings have been reported even for the association between DAT binding and ADHD (Jucaite et al., 2005; Volkow et al., 2007). Moreover, our data is agreement with theories suggesting that ADHD

symptoms and response to MPH might not be totally accounted by dopaminergic circuits (Volkow et al., 2007; Gainetdinov et al., 1999).

Our study should be understood in the context of some limitations. Our sample included individuals who had a SUD diagnosis for more than one drug category (cannabis and cocaine). However, we also analyzed the data separately, according to the presence of cocaine use, and the direction of the findings were the same. Also, approximately 25% of the sample had an AUD, thus we were not dealing with just cannabis and/or cocaine use. In addition, ADHD severity measure relied on SNAP-IV scale, without laboratorial measures of attention/impulsivity. We had a small sample size, limiting the power for some analyses (e.g., assessment of interactions) and findings can not be generalized to female gender, adults or adolescents with a different pattern of drug use. Also, we had no measures of MPH plasma levels. Despite these caveats, to the best of our knowledge, this was the first study to evaluate stimulant effects on striatal DAT density in a non abstinent sample of adolescents with ADHD/SUD.

In conclusion, the most important finding of this study was that MPH keeps binding to DAT even under current drug use in adolescents, and after several months of abuse/dependence of drugs. This data support the rationale for stimulants clinical trials in adolescents with ADHD+SUD.

Acknowledgments: this work was partially supported by research grants from: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) (Grant 307780/2004-0); Hospital de Clínicas de Porto Alegre. Toxilab® provided urinary assays. Medication was provided by NOVARTIS at no cost and without restrictions.

Potential conflict of interests: The ADHD outpatient program receives research support from the following pharmaceutical companies: Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag, and Novartis. Prof Rohde is on the speakers' bureau or is a consultant for the same companies and is on the advisory board for Eli Lilly & Company. DR. Szobot is on the speakers' bureau of Janssen-Cilag and had travel support by Novartis. Dr. Bressan is on the speakers' bureau or is a consultant for Eli Lilly, Astra-Zeneca, Janssen and Novartis. Dr. Pechansky: Dr. Pechansky's center receives funding for research projects from NIDA, NIAID, and the Brazilian Anti-Drug Secretaria. All other authors (Dr. Ming Chi Shih, Thais Schaefer, Dr. Neivo Júnior, Marcelo Q. Hoexter and Ying Kai Fu) have no conflict of interest to declare.

REFERENCES

1. Polanczyk, G., Horta, B., Lima, M., Biederman, J., Rohde, LA., 2007. The worldwide prevalence of ADHD. A systematic review and meta-regression analysis. Am J Psychiatry 164(6):942-8.

2. American Psychiatric Association., 1994. Diagnostic and Statistical Manual of Mental Disorders, (4th edition). Washington, DC, American Psychiatric Association.

3. Spencer, T.,J., Biederman, J., Mick, E., 2007. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. Ambul Pediatr 7(1 Suppl):73-81.

4. Molina, B.,S.,G.,M., Smith, B.,H., Pelham, W.,E., 1999. Interactive effects of Attention Deficit Hyperactivity Disorder and Conduct Disorder on early adolescent substance use. Psychology of Addictive Behs. 13:348-358.

5. Biederman, J., Monuteaux, M.,C., Mick, E., Spencer, T., Wilens, T.,E,, Silva, J.,M., Snyder, L.,E., Faraone, S.,V., 2006.Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol Med 36(2):167-79.

6. Szobot, C., Rohde, L.,A., Bukstein, O., Molina, B.,S.,G., Martins, C., Ruaro, P., Pechansky, F., 2007. Is Attention-Deficit/ Hyperactivity Disorder associated with illicit Substance Use Disorders in male adolescents? A community-based case-control study. Addiction 102(7):1122-1130.

7. DeMilio, L., 1989. Psychiatric syndromes in adolescent substance abusers. Am J Psychiatry 46(9):1212-4.

8. Kuperman, S., Schlosser, S.,S., Kramer, J.,R., Bucholz, K., Hesselbrock, V., Reich, T., Reich, W., 2001.Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. Am J Psychiatry 158(12):2022-6.

9. Horner, B.,R., Scheibe, K.,E., 1997. Prevalence and implications of attention-deficit hyperactivity disorder among adolescents in treatment for substance abuse. J Am Acad Child Adolesc Psychiatry 36(1):30-6.

10. Ercan, E.,S., Coskunol, H., Varan, A., Toksoz, K., 2003. Childhood attention deficit/hyperactivity disorder and alcohol dependence: a 1-year follow-up. Alcohol Alcohol 38(4):352-6.

11. White, A.,M., Jordan, J.,D., Schroeder, K.,M., Acheson, S.,K., Georgi, B.,D., Sauls, G., Ellington, R.,R., Swartzwelder, H.,S., 2004. Predictors of relapse during treatment and treatment completion among marijuana-dependent adolescents in an intensive outpatient substance abuse program. Subst Abus 25(1):53-9.

12. Pliszka, S.,R., Crismon, M.,L., Hughes, C.,W., Corners, C.,K., Emslie, G.,J., Jensen, P.,S., McCracken, J.,T., Swanson, J.,M., Lopez, M., 2006.Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 45(6):642-57.

13. Spencer, T.,J., Biederman, J., Ciccone, P.,E., Madras, B.,K., Dougherty, D.,D., Bonab, A.,A., Livni, E., Parasrampuria, D.,A., Fischman, A.,J, 2006. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry 163(3):387-95.

14. Volkow, N.,D., Fowler, J.,S., Wang, G.,J., 2004. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology 47 Suppl 1:3-13.

15. Rodriguez de Fonseca, F., Del Arco, I., Bermudez-Silva, F.,J., Bilbao, A., Cippitelli, A., Navarro, M., 2005. The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol 40(1):2-14.

16. Koob, G.,F., 2006.The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. Addiction 101 Suppl 1:23-30.

17. Tzavara, E.,T., Li, D.,L., Moutsimilli, L., Bisogno, T., Di Marzo, V., Phebus, L.,A., Nomikos, G.,G., Giros, B., 2006. Endocannabinoids activate transient receptor potential vanilloid 1 receptors to reduce hyperdopaminergia-related hyperactivity: therapeutic implications. Biol Psychiatry 15;59(6):508-15.

18. Carpentier, P.,J., de Jong, C.,A., Dijkstra, B.,A., Verbrugge, C.,A., Krabbe, P.,F., 2005. A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. Addiction 100(12):1868-74.

19. Levin, F.,R., Evans, S.,M., Brooks, D.,J., Garawi, F., 2007. Treatment of cocaine dependent treatment seekers with adult ADHD: Double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend 87(1):20-9.

20. Levin, F.,R., Evans, S.,M., Brooks, D.,J., Kalbag, A.,S., Garawi, F., Nunes, E.,V., 2006. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug Alcohol Depend 81(2):137-48.

21. Krain, A.,L., Castellanos, F.,X., 2006. Brain development and ADHD. Clin Psychol Rev 26(4):433-44.

22. Dougherty, D.,D., Bonab, A.,A., Spencer, T.,J., Rauch, S.,L., Madras, B.,K., Fischman, A.,J., 1999. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 18-25;354(9196):2132-3.

23. Larisch, R., Sitte, W., Antke, C., Nikolaus, S., Franz, M., Tress, W., Muller, H.,W., 2006. Striatal dopamine transporter density in drug naive patients with attention-deficit/hyperactivity disorder. Nucl Med Commun 27(3):267-70.

24. Schlaepfer, T.,E., Pearlson, G.,D., Wong, D.,F., Marenco, S., Dannals, R.,F., 1997. PET study of competition between intravenous cocaine and [11C]raclopride at dopamine receptors in human subjects. Am J Psychiatry 154(9):1209-13.

25. Volkow, N.,D., Ding, Y.,S., Fowler, J.,S., Wang, G.,J., Logan, J., Gatley, J.,S., Dewey, S., Ashby, C., Liebermann, J., Hitzemann, R., et al. 1995.Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry 52(6):456-63.

26. Dresel, S., Krause, J., Krause, K.,H., LaFougere, C., Brinkbaumer, K., Kung, H.,F., Tatsch, K., 2000. Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. Eur J Nucl Med 27(10):1518-24.

27. la Fougère, C., Krause, J., Krause, K.,H., Josef, G.,F., Hacker, M., Koch, W., Hahn, K., Tatsch, K., Dresel, S., 2006. Value of 99mTc-TRODAT-1 SPECT to predict clinical response to methylphenidate treatment in adults with attention deficit hyperactivity disorder. Nucl Med Commun 27(9):733-7.

28. Krause, J., la Fougere, C., Krause, K.,H., Ackenheil, M., Dresel, S.,H., 2005. Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD. Eur Arch Psychiatry Clin Neurosci 255(6):428-31.

29. World Health Organization (WHO): available at http://www.who.int/substance_abuse/facts/cannabis/en/index.html (assessed January 08, 2006).

30. Price, D.,A., Owens, W.,A., Gould, G.,G., Frazer, A., Roberts, J.,L., Daws, L.,C., Giuffrida, A., 2007. CB(1)-independent inhibition of dopamine transporter activity by cannabinoids in mouse dorsal striatum. J Neurochem 101(2):389-96.

31. Liu, F., Muniz, R., Minami, H., Silva, R.,R., 2005. Review and comparison of the long acting methylphenidate preparations. Psychiatr Q 76(3):259-69.

32. Mercadante, M.,T., Asbarch, F., Rosário, M.,C., Ayres, A.,M., Ferrari, M.,C., Assumpção, F.,B., et al., 1995. K-SADS, 1º edição. São Paulo, SP: Protoc – Hospital das Clínicas da FMUSP.

33. Rohde, L.,A., Szobot, C., Polanczyk, G., Schmitz, M., Martins, S., Tramontina, S., 2005. Attention-deficit/hyperactivity disorder in a diverse culture: do research and clinical findings support the notion of a cultural construct for the disorder? Biol Psychiatry 1;57(11):1436-41.

34. Amorim, P., 2000). Mini International Neuropsychiatric Interview (MINI): Validação de entrevista breve para diagnóstico de transtornos mentais. Revista Bras Psiquiatr 22:106-115.

35. Associação Brasileira de Empresas de Pesquisas. Critério de Classificação Econômica Brasil., 2005. Available at http://www.anep.org.br/codigosguias/CCEP.pdf (assessed April 18, 2005).

36. Wechsler, D., 1991. WISC-III/Manual. New York, NY: The Psychological Corporation.

37. Wechsler, D., 1997. Manual of the Wechsler Adult Intelligence Scale (3rd edition). San Antonio TX: The Psychological Corporation.

38. Shaffer, D., Gould, M.,S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., Aluwahlia, S., 1983: A children's global assessment scale (CGAS). Arch Gen Psychiatry 40:1228-31.

39. Swanson, J.,M., Kraemer, H.,C., Hinshaw, S.,P., Arnold, L.,E., Conners, C.,K., Abikoff, H.,B., Clevenger, W., Davies, M., Elliott, G.,R., Greenhill, L.,L., Hechtman, L., Hoza, B., Jensen, P.,S., March, J.,S., Newcorn, J.,H., Owens, E.,B., Pelham, W.,E., Schiller, E., Severe, J.,B., Simpson, S., Vitiello, B., Wells, K., Wigal, T., Wu, M., 2001. Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 40(2):168-79.

40. Mattos, P., Serra Pinheiro, M.,A., Rohde, L.,A., Pinto, D., 2006. A Brazilian version of the MTA-SNAP-IV for evaluation of symptoms of attention-deficit/hyperactivity disorder and oppositional-defiant disorder. Rev. psiquiatr. Rio Gd. Sul 28(3)290-297..

41. Choi, S.,R., Kung, M.,P., Plossl, K., Meegalla, S., Kung, H.,F., 1999. An improved kit formulation of a dopamine transporter imaging agent: [Tc-99m]TRODAT-1. Nucl Med Biol 26:461-466.

42. Krause, K.,H., Dresel, S.,H., Krause, J., Kung, H.,F., Tatsch, K., Ackenheil, M., 2002. Stimulant-like action of nicotine on striatal dopamine transporter in the brain of adults with attention deficit hyperactivity disorder. Int J Neuropsychopharmacol 5(2):111-3.

43. Krause, K.,H., Dresel, S.,H., Krause, J., Kung, H.,F., Tatsch, K., 2000. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett 12;285(2):107-10.

44. Cowell, R.,M., Kantor, L., Hewlett, G.,H., Frey, K.,A., Gnegy, M.,E., 2000. Dopamine transporter antagonists block phorbol ester-induced dopamine release and dopamine transporter phosphorylation in striatal synaptosomes. Eur J Pharmacol 389(1):59-65.

45. Daws, L.,C., Callaghan, P.,D., Moron, J.,A., Kahlig, K.,M., Shippenberg, T.,S., Javitch, J.,A., Galli, A., 2002. Cocaine increases dopamine uptake and cell surface expression of dopamine transporters. Biochem Biophys Res Commun 8;290(5):1545-50.

46. Herkenham, M., Lynn, A.,B., Little, M.,D., Johnson, M.,R., Melvin, L.,S., de Costa, B.,R., Rice, K.,C., 1990. Cannabinoid receptor localization in brain. Proc Natl Acad Sci USA 87(5):1932-6.

47. Koob, G.,F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278(5335):52-8.

48. Volkow, N.,D., Wang, G.,J., Fowler, J.,S., Telang, F., Maynard, L., Logan, J., Gatley, S.,J., Pappas, N., Wong, C., Vaska, P., Zhu, W., Swanson, J.,M., 2004. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. Am J Psychiatry 161(7):1173-80.

49. Stansfield, K.,H., Kirstein, C.,L., 2005. Neurochemical effects of cocaine in adolescence compared to adulthood. Brain Res Dev Brain Res 6;159(2):119-25.

50. Badanich, K.,A., Adler, K.,J., Kirstein, C.,L., 2006. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. Eur J Pharmacol 21;550(1-3):95-106.

51. Volkow, N.,D., Wang, G.,J., Fowler, J.,S., Gatley, S.,J., Logan, J., Ding, Y.,S., Hitzemann, R., Pappas, N., 1998. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 155(10):1325-31.

52. Jucaite, A., Fernell, E., Halldin, C., Forssberg, H., Farde, L., 2005. Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: association between striatal dopamine markers and motor hyperactivity. Biol Psychiatry 1;57(3):229-38.

53. Volkow, N.,D., Wang, G.,J., Newcorn, J., Fowler, J.,S., Telang, F., Solanto, M.,V., Logan, J., Wong, C., Ma, Y., Swanson, J.,M., Schulz, K., Pradhan, K., 2007. Brain dopamine transporter levels in treatment and drug naive adults with ADHD. Neuroimage 1;34(3):1182-90.

54. Gainetdinov, R.,R., Wetsel, W.,C., Jones, S.,R., Levin, E.,D., Jaber, M., Caron, M.,G., 1999. Role of serotonin in the paradoxical calming effect os psychoestimulants on hyperactivity. Science 283:397-401.

Table 8 (1) - Demographic, clinical characteristics, IQ and drug use in 17 adolescents with ADHD comorbid with illicit SUD

Characteristics	Results	
	Means (SD)	n(%)
Age (years)	17.24 (2.28)	
Ethnicity (European-Brazilian)		12 (70.6)
Estimated IQ	85.47 (20.49)	
CGAS (baseline score)	41.47 (9.15)	
SNAP-IV (baseline score)	49.18 (14.12)	
Further Lifetime DSM-IV Axis I diagnoses		
Major Depression		3 (17.64)
Conduct Disorder		13 (76.47)
Oppositional Defiant Disorder		6 (35.29)
Separation Anxiety Disorder		1 (5.8)
Enuresis		1 (5.8)
Age at first cannabis use	13.0 (2.07)	
Age at first cocaine use	14.67 (2.44)	
SUD for cannabis		17 (100)
SUD for cocaine		5 (29.41)
Months with regular use of cannabis*	37.75 (27.45)	
Days with cannabis use, last month*	26.94 (6.90)	
Months with regular use of cocaine**	26.50 (29.65)	
Days with snorted cocaine, last month**	5.50 (4.44)	
Months with regular use of crack**	17.0 (12.73)	
Days with crack use, last month**	21.50 (9.19)	
Urinary test positive for cannabis		13 (76.47)
Urinary test positive for cannabis and cocaine		2 (11.76)
Urinary test positive for cocaine		1 (5.8)
Negative urinary test		1 (5.8)
Nicotine smokers		16 (94.1)
Number of nicotine cigarettes/day**	15.88 (7.71)	
Days with drug use, last week	6.29 (1.69)	

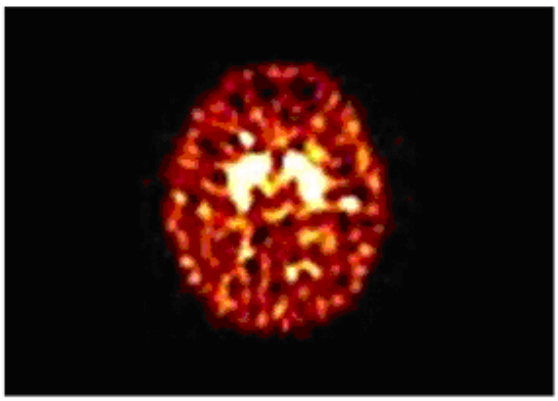
Note: *IQ* = Intelligence quotient; *ADHD* = Attention Deficit/ Hyperactivity Disorder; *SUD* = Substance Use Disorder; *CGAS* = Clinical Global Assessment Scale; *= include all subjects; ** = include just subjects with regular use of the mentioned drug; *SNAP-IV* = Swanson, Nolan and Pelham Scale – version IV.

Table 9 (2) - Changes in TRODAT1-binding, ADHD symptoms and drug use after 3 weeks on MPH-SODAS in a sample of 17 adolescents with ADHD comorbid with illicit SUD

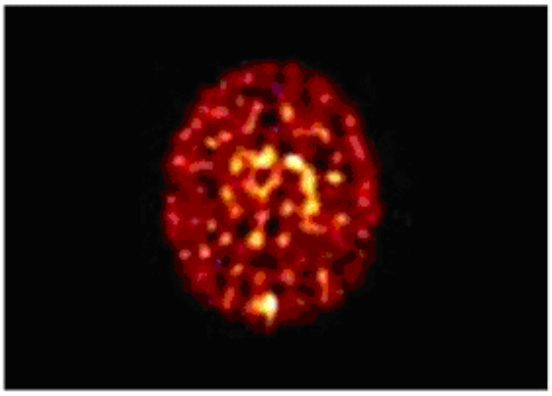
	Baseline Mean (SD)	After 3 weeks on MPH-SODAS Mean (SD)	P value*
Striatal TRODAT-1 binding			
Left caudate	1.16 (0.17)	0.54 (0.28)	< .001
Left putamen	1.09 (0.21)	0.51 (0.21)	< .001
Right caudate	1.08 (0.23)	0.49 (0.30)	< .001
Right putamen	1.04 (0.19)	0.49 (0.20)	< .001
SNAP-IV			
Total	49.18 (14.12)	22.24 (12.24)	< .001
Inattentive	17.84 (6.51)	7.41 (7.70)	< .001
Hyperactivity/Impulsivity	19.47 (6.18)	9.41 (6.67)	< .001
Drug use**	6.29 (1.69)	4.94 (2.46)	< .01

Note: *ADHD* = Attention Deficit/ Hyperactivity Disorder; MPH-SODAS: long action formulation of methylphenidate; *SUD* = Substance Use Disorder; *SNAP-IV* = Swanson, Nolan and Pelham Scale – version IV; *t test for paired samples; **Number of days with reported drug use/week.

Figure 4 (1) – Caudato and Putamen TRODAT1-binding in a 15 years adolescent with ADHD + SUD for cannabis, before and after 3 weeks on MPH-SODAS



Baseline:
SNAP-IV = 72
TRODAT binding: LC= 0.99; RC= 1.00
LP= 0.81; RP= 0.92
Cannabis use: 7 days/week;
Nicotine use: 20 cigarettes/day



On MPH:
SNAP-IV = 43
TRODAT binding: LC= 0.49; RC= 0.56
LP= 0.43; RP= 0.62
No change in cannabis and nicotine use

Note: ADHD = Attention Deficit/ Hyperactivity Disorder; SUD = Substance Use Disorder; SNAP-IV = Swanson, Nolan and Pelham Scale – version IV; MPH = methylphenidate SODAS; PLA = Placebo; LC = Left Caudato; RC = Right Caudato; LP = Left Putamen; RP = Right Putamen.

8 CONCLUSÃO

Este projeto de pesquisa teve como produtos diretos os três artigos apresentados anteriormente, sendo que um deles já está publicado. O segundo e o terceiro artigos estão aceitos para puplicação, *in press*.

O primeiro artigo demonstrou que, no nosso contexto, o TDAH sem tratamento pode ser considerado um fator de risco independente para o TUSP em adolescentes masculinos. Este dado reforça a necessidade da identificação precoce do TDAH, para que a criança receba um tratamento adequado que, possivelmente, diminuirá as suas chances de desenvolver TUSP. Além disso, se crianças com TDAH apresentam risco aumentado de TUSP, campanhas de prevenção primária ao TUSP devem ser incentivadas desde cedo nesta população, contemplando as características cognitivas e comportamentais do TDAH. Os achados deste estudo também são muito importantes no sentido de orientação aos pais, que muitas vezes têm receio de administrar o metilfenidato (MFD) aos filhos. Nossos dados confirmam a linha de entendimento de que é a ausência de tratamento que deve gerar preocupações (como TUSP futuro), e não o tratamento em si, uma vez que o risco do TDAH não tratado supera o risco eventual do potencial de abuso do MFD em crianças tratadas com esta medicação. A base epidemiológica que serviu para identificar casos e controles na comunidade foi utilizada para o mestrado de colega do CPAD, que re-entrevistou parte da amostra no intuito de estudar a associação entre impulsividade, idade de primeiro consumo de álcool e TUSP (resultado deste mestrado: um artigo publicado na Revista Brasileira de Psiquiatria e outro in press, *Addiction*).

O segundo artigo é um trabalho pioneiro, visto que até o momento não há dados publicados sobre a efetividade do MFD em adolescentes com TDAH e TUSP. Uma força deste estudo foi ter incluído pacientes não internados, com uso de mais de um tipo de substância psicoativa (SPAs), correspondendo à realidade da maioria dos jovens com TUSP. Demonstramos a superioridade do MFD em relação ao placebo, e não tivemos maiores intercorrências, assim estimulando a execução de mais protocolos de pesquisa neste enfoque. Entretanto, é importante destacar que neste estudo observarmos o distanciamento que pode existir entre sujeitos que ingressam em um protocolo clínico e o total de sujeitos acometidos pelo transtorno alvo na população geral: dos 27 adolescentes do estudo de caso-controle que atendiam critérios de elegibilidade ao *crossover*, apenas 14 aceitaram ingressar no estudo medicamentoso. Apesar de nosso tamanho amostal ser pequeno para maiores explorações sobre possíveis diferenças entre quem aceitou ou não receber tratamento para o TDAH, constatamos que a gravidade do TDAH, de acordo com o SNAP-IV, era semelhante entre os dois grupos ($p = 0.36$).

O terceiro artigo demonstrou, pela primeira vez, como que em sujeitos com TDAH o MFD se liga ao DAT em um contexto de uso de SPAs, visto que muitas delas ou competem com o MFD pelo DAT, ou causam alterações dopaminérgicas. Constatamos que o MFD segue se ligando ao DAT, mesmo em sujeitos não abstinentes. Este é um dado de suma importância, pois fortalece a base teórica dos estudos com estimulantes com sujeitos com TDAH e TUSP, área cujo tratamento farmacológico carece claramente de mais estudos - sobretudo em adolescentes. Além disso, apesar de haver na literatura vários estudos de neuroimagem em TDAH e vários outros em TUSP, não identificamos estudos de NI avaliando especificamente sujeitos com TDAH e TUSP, aumentando a relevância do nosso estudo. Este estudo iniciou uma parceria do CPAD e do PRODAH com a UNIFESP e com a Irmandande Santa Casa de Miseridórdia, que até hoje se sustenta a partir de outros projetos iniciados colaborativamente.

Também, pela primeira vez tivemos a oportunidade de trabalhar, em NI, com marcador dopaminérgico [Tc^{99m}]TRODAT-1, significando a aquisição de uma nova tecnologia.

No primeiro artigo apresentado nos anexos (Anexo 1), foi possível fazer uma revisão da literatura a respeito da comorbidade TDAH e TUSP. Neste material, foi possível abordar mais especificamente algumas questões que, apesar de bastante estudadas ao longo desta linha de pesquisa, não foram suficientemente contempladas nos artigos principais da tese, por distanciarem-se um pouco dos seus focos. É o caso, por exemplo, do potencial de abuso do MFD. Da mesma forma, o capítulo de livro sobre as bases neurobiológicas do TUSP em adolescentes (Anexo 2) explorou mais detalhadamente outras questões que contribuem para a etiologia do TUSP em adolescentes, além de revisar aspectos gerais de tratamento de adolescentes com TUSP.

O presente projeto teve algumas peculiaridades que devem ser destacadas. Inicialmente, apesar da alta prevalência de TUSP em adolescentes, a realidade no Brasil é de pouca pesquisa nesta área e, sobretudo, de uma escassa rede de atendimento a tais pacientes. Assim, um projeto focalizado em TUSP na adolescência ajuda a preencher uma séria lacuna existente no nosso meio, ressaltando a importância do tema desta tese. Também, trabalhamos no estudo de caso-controle com amostra comunitária; observamos que, infelizmente, de todos os sujeitos com TDAH, nenhum havia sido diagnosticado previamente (apesar dos altos valores no SNAP-IV), fortalecendo a idéia de que, no nosso contexto, a realidade é de subdiagnóstico de TDAH. Observamos, também, que os adolescentes, quando abordados de forma adequada, relatam claramente o seu uso de SPAs (a taxa de recusa foi baixa, e todos sabiam que as suas informações seriam checadas por teste de urina). Da mesma forma, pouquíssimos adolescentes com TUSP tiveram experiência prévia de tratamento para este transtorno, apesar de muitos demonstrarem interesse, ressaltando novamente a escassez de atendimento adequado a essa população.

Outra questão que merece destaque é que esse projeto contou, sistematicamente, com a participação de dois grupos de pesquisa (Centro de Pesquisa em Álcool e Drogas e Programa de Déficit de Atenção, ambos do Hospital de Clínicas de Porto Alegre), assim unindo prática de pesquisa com dependência química, com prática de pesquisa em infância e adolescência. Ao longo do projeto, foi estabelecida uma colaboração com a Universidade de Pittsburgh, conceituado centro de pesquisa em dependência química na adolescência. Foi realizado um estágio de dois meses no referido serviço, tendo o Dr. Bukstein como mentor, no sentido de melhor compreender técnicas de avaliação, tratamento e pesquisa em adolescentes com TUSP, já que no nosso meio não há profissionais com essa formação combinada (Psiquiatria de Infância e Adolescência e dependência química).

Destaca-se, também, que a parceria iniciada entre o CPAD e o PRODAH em pesquisa na comorbidade TDAH e TUSP tem seguimento a partir de um projeto escrito para fins do Exame Geral de Qualificação da presene aluna. O referido projeto, que visa avaliar a prevalência de TDAH e TUSP em *motoboys*, bem como o efeito do tratamento com MFD sobre a habilidade em dirigir, em *motoboys* com TDAH, já está em fase de colea de dados.

Em suma, além de fornecer dados novos à literatura em uma área ainda incipiente, este projeto permitiu: a) iniciar uma linha de pesquisa em TUSP na adolescência; b) aprendizado de novas técnicas de pesquisa de NI (SPECT com TRODAT-1), até então inéditas nos nossos grupos; c) vínculo colaborativo com conceituado centro de atendimento e pesquisa em TUSP na adolescência (Universidade de Pittsburgh), que se sustenta atualmente (vide anexos); d) inicio de vínculo colaborativo com UNIFESP e Santa Casa de Misericórdia; e) contribuir para a elaboração de um mestrado; f) iniciar outro projeto na comorbidade TDAH/TUSP, agora com população de *motoboys*.

9 REFERÊNCIAS BIBLIOGRÁFICAS

AACAP OFFICIAL ACTION. Practice parameters for the use of stimulant medication in the treatment of children, adolescents, and adults. **J Am Acad Adolesc Psychiatry**, v. 41, n. 2, p. 26S-49S, 2002.

AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY (AACAP). Practice parameters for the assessment and treatment of children, adolescents and adults with attention – deficit / hyperactivity disorder. **J Am Acad Adolesc Psychiatry**, v. 36, p. 85S-121S, 1997.

AMERICAN ACADEMY OF PEDIATRICS: Clinical Practice Guideline: Treatment of school age children with ADHD. **Pediatrics**, v. 108, p. 1033-1044, 2001.

AMERICAN PSYCHIATRIC ASSOCIATION. **Diagnostic and Statistical Manual of Mental Disorders**. 4. ed. Washington, DC: American Psychiatric Association, 1994.

ARON, A. R.; POLDRACK, R. A. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. **Biol Psychiatry**, v. 57, p. 1285-1292, 2005.

AUGUST, G. J.; WINTERS, K. C.; REALMUTO, G. M.; FAHNHORST, T.; BOTZET, A.; LEE, S. Prospective study of adolescent drug use among community samples of ADHD and non-ADHD participants. **J Am Acad Child Adolesc Psychiatry**, v. 45, n. 7, p. 824-832, 2006.

BABCOCK, Q.; BYRNE, T. Student perceptions of methylphenidate abuse at a public liberal arts college. **Am Coll Health**, v. 49, n. 3, p. 143-145, 2000.

BADANICH, K. A.; ADLER, K. J.; KIRSTEIN, C. L. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. **Eur J Pharmacol**, v. 21, n. 550(1-3), p. 95-106, 2006.

BARKLEY, R. A. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. **J Clin Psychiatry**, v. 63, n. 12, p. 10-15, 2002.

BARKLEY, R. A.; FISCHER, M.; SMALLISH, L.; FLETCHER, K. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. **Pediatrics**, v. 111, n. 1, p. 97-109, 2003.

BIEDERMAN, J.; MONUTEAUX, M. C.; MICK, E.; SPENCER, T.; WILENS, T. E.; SILVA, J. M.; SNYDER, L. E.; FARAONE, S. V. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. **Psychol Med**, v. 36, n. 2, p. 167-179, 2006.

BIEDERMAN, J.; NEWCORN, J.; SPRICH, S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. **Am J Psychiatry**, v. 148, p. 564-577, 1991.

BIEDERMAN, J.; WILENS, T.; MICK, E.; SPENCER, T.; FARAONE, S. V. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. **Pediatrics**, v. 104, n. 2, p. e20, 1999.

BIERDERMAN, J.; WILENS, T. E.; MICK, E.; FARAONE, S. V.; SPENCER, T. Does attention-deficit hyperactivity disorder impact the developmental course of drug and alcohol abuse and dependence? **Biol Psychiatry**, v. 44, n. 4, p. 269-273, 1998.

BIERDERMAN, J.; WILENS, T.; MICK, E.; FARAONE, S. V.; WEBER, W.; CURTIS, S.; THORNELL, A.; PFISTER, K.; JETTON, J. G.; SORIANO, J. Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. **J Am Acad Child Adolesc Psychiatry**, v. 36, n. 1, p. 21-29, 1997.

BIERDERMAN, J.; WILENS, T.; MICK, E.; MILBERGER, S.; SPENCER, T. J.; FARAONE, S. V. Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): effects of ADHD and psychiatric comorbidity. **Am J Psychiatry**, v. 152, n. 11, p. 1652-1658, 1995.

BUKSTEIN, O.G.; GLANCY, L.J.; KAMINER, Y. Patterns of affective comorbidity in a clinical population of dually diagnosed adolescent substance abusers. J Am Acad Child Adolesc Psychiatry, v.31, n.6, p.1041-5, 1992.

CARPENTIER, P. J.; DE JONG, C. A.; DIJKSTRA, B. A.; VERBRUGGE, C. A.; KRABBE, P. F. A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. **Addiction**, v. 100, n. 12, p. 1868-1874, 2005.

CARROLL, K. M.; ROUNSAVILLE, B. J. History and significance of childhood attention deficit disorder in treatment-seeking cocaine abusers. **Compr Psychiatry**, v. 34, n. 2, p. 75-82, 1993.

CLARK, D. B.; POLLOCK, N.; BUKSTEIN, O. G.; MEZZICH, A. C.; BROMBERGER, J. T.; DONOVAN, J. E. Gender and comorbid psychopathology in adolescents with alcohol dependence. **J Am Acad Child Adolesc Psychiatry**, v. 36, n. 9, p. 1195-1203, 1997.

COSTELLO, E. J.; EGGER, H.; ANGOLD, A. 10-year research update review: the epidemiology of child and adolescent psychiatric disorders: I. Methods and public health burden. J Am Acad Child Adolesc Psychiatry. 2005 Oct;44(10):972-86.

DEMILIO, L. Psychiatric syndromes in adolescent substance abusers. **Am J Psychiatry**, v. 146, n. 9, p. 1212-1214, 1989.

DISNEY, E. R.; ELKINS, I. J.; MCGUE, M.; JACONO, W. G. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. **Am J Psychiatry**, v. 156, n. 10, p. 1515-1521, 1999.

DRESEL, S.; KRAUSE, J.; KRAUSE, K. H.; LAFOUGERE, C.; BRINKBAUMER, K.; KUNG, H. F.; TATSCH, K. Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. **Eur J Nucl Med**, v. 27, n. 10, p. 1518-1524, 2000.

ELKINS, I. J.; McGUE, M.; IACONO, W. G. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. **Arch Gen Psychiatry**, v. 64, p. 1145-1152, 2007.

ERCAN, E.S.; COSKUNOL, H.; VARAN, A.; TOKSOZ, K. Childhood attention deficit/hyperactivity disorder and alcohol dependence: a 1-year follow-up. **Alcohol Alcohol**, v. 38, n. 4, p. 352-356, 2003.

FERGUSSON, D. M.; HORWOOD, L. J.; RIDDER, E. M. Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. **Drug Alcohol Depend**, v. 88, suppl 1, p. S14-S26. 2007.

FISCHER, M.; BARKLEY, R. A.; SMALLISH, L.; FLETCHER, K. Executive functioning in hyperactive children as young adults: attention, inhibition, response perseveration, and the impact of comorbidity. **Dev Neuropsychol**, v. 27, p. 107-133, 2005.

GAINETDINOV, R. R.; WETSEL, W. C.; JONES, S. R.; LEVIN, E. D.; JABER, M.; CARON, M. G. Role of serotonin in the paradoxical calming effect os psychoestimulants on hyperactivity. **Science**, v. 283, p. 397-401, 1999.

GALDUROZ, J. C.; NOTO, A. R.; NAPPO, S. A.; CARLINI, E. A. Household survey on drug abuse in Brazil: study involving the 107 major cities of the country--2001. **Addict Behav**, v. 30, p. 545-556, 2005.

GAU, S. S.; CHONG, M. Y.; YANG, P.; YEN, C. F.; LIANG, K. Y.; CHENG, A. T. Psychiatric and psychosocial predictors of substance use disorders among adolescents: longitudinal study. **Br J Psychiatry**, v. 190, p. 42-48, 2007.

GORDON, S. M.; TULAK, F.; TRONCALE, J. Prevalence and characteristics of adolescents patients with co-occurring ADHD and substance dependence. **J Addict Dis**, v. 23, n. 4, p. 31-40, 2004.

GREENHILL, L. L.; HALPERIN, J. M.; ABIKOFF, H. Stimulant medications. **J Am Acad Child Adolesc Psychiatry**, v. 38, n. 5, p. 503-512, 1999.

GUINDALINI, C.; HOWARD, M.; HADDLEY, K.; LARANJEIRA, R.; COLLIER, D.; AMMAR, N.; CRAIG, I.; O'GARA, C.; BUBB, V.J.; GREENWOOD, T.; KELSOE, J.; ASHERSON, P.; MURRAY, R.M.; CASTELO, A.; QUINN, J.P.; VALLADA, H.; BREEN, G. A dopamine transporter gene functional variant associated with cocaine abuse in a Brazilian sample. **Proc Natl Acad Sci U.S.A.**, v. 21, n. 103(12), p. 4552-4557, 2006.

HORNER, B. R.; SCHEIBE, K. E. Prevalence and implications of attention-deficit hyperactivity disorder among adolescents in treatment for substance abuse. **J Am Acad Child Adolesc Psychiatry**, v. 36, n.1, p. 30-36, 1997.

KALIVAS, P. W.; VOLKOW, N. D. The neural basis of addiction: a pathology of motivation and choice. **Am J Psychiatry**, v. 162, p. 1403-1413, 2005.

KESSLER, R. C.; ADLER, L.; BARKLEY, R.; BIEDERMAN, J.; CONNERS, C. K.; DEMLER, O.; FARAONE, S. V.; GREENHILL, L. L.; HOWES, M. J.; SECNIK, K.; SPENCER, T.; USTUN, T. B.; WALTERS, E. E.; ZASLAVSKY, A. M. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. **Am J Psychiatry**, v. 163, n. 4, p. 716-723, 2006.

KLEIN-SCHWARTZ, W.; McGRATH, J. Poison centers´ experience with methylpnhenidate abuse in pre-teens and adolescents. **J Am Acad Adolesc Psychiatry**, v. 42, p. 288-294, 2003.

KOOB, G. F. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. **Addiction**, v. 101, suppl 1, p. 23-30, 2006.

KRAIN, A. L.; CASTELLANOS, F. X. Brain development and ADHD. **Clin Psychol Rev**, v. 26, n. 4, p. 433-444, 2006.

KRAUSE, J.; LA FOUGERE, C.; KRAUSE, K. H.; ACKENHEIL, M.; DRESEL, S. H. Influence of striatal dopamine transporter availability on the response to methylphenidate in adult patients with ADHD. **Eur Arch Psychiatry Clin Neurosci**, **v.** 255, n. 6, p. 428-431, 2005.

KUPERMAN, S.; SCHLOSSER, S. S.; KRAMER, J. R.; BUCHOLZ, K.; HESSELBROCK, V.; REICH, T.; REICH, W. Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. **Am J Psychiatry**, v. 158, n. 12, p. 2022-2026, 2001.

LA FOUGÈRE, C.; KRAUSE, J.; KRAUSE, K. H.; JOSEF, G. F.; HACKER, M.; KOCH, W.; HAHN, K.; TATSCH, K.; DRESEL, S. Value of 99mTc-TRODAT-1 SPECT to predict clinical response to methylphenidate treatment in adults with attention deficit hyperactivity disorder. **Nucl Med Commun**, v. 27, n. 9, p. 733-737, 2006.

LAMBERT, N. M.; HARTSOUGH, C. S. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. **J Learn Disabil**, v. 31, n. 6, p. 533-544, 1998.

LEVIN, F. R.; EVANS, S. M.; BROOKS, D. J.; GARAWI, F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend., v. 87, n. 1, p. 20-29, 2007.

LEVIN, F. R.; EVANS, S. M.; MCDOWELL, D. M.; KLEBER, H. D. Methylphenidate treatment for cocain abusers with adult attention-deficit/hyperactivity disorder: a pilot study. **J Clin Psychiatry**, v. 59, p. 300-305, 1998.

MANNUZZA, S.; KLEIN, R. G.; BONAGURA, N.; MALLOY, P.; GIAMPINO, T. L.; ADDALLI, K. A. Hyperactive boys almost grown up. V. Replication of psychiatric status. **Arch Gen Psychiatry**, v. 48, n. 1, p. 77-83, 1991.

MANNUZZA, S.; KLEIN, R. G.; MOULTON, J. L. Persistence of attention-deficit/hyperactivity disorder into adulthood: what have we learned from the prospective follow-up studies? **J Atten Disord**, v. 7, n. 2, p. 93-100, 2003.

MANNUZZA, S.; KLEIN, R.; BESSLER, A.; MALLOY, P.; LAPADULA, M. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. **Arch Gen Psychiatry**, v. 50, n. 7, p. 565-576, 1993.

MANNUZZA, S.; KLEIN, R.; BESSLER, A.; MALLOY, P.; LAPADULA, M. Adult psychiatric status of hyperactive boys grown up. **Am J Psychiatry**, v. 155, n. 4, p. 493-498, 1998.

MARTIN, C. A.; GUENTHNER, G.; BINGCANG, C.; RAYENS, M. K.; KELLY, T. H. Measurement of the subjective effects of methylphenidate in 11- to 15-year-old children with attention-deficit/hyperactivity disorder. **J Child Adolesc Psychopharmacol**, v. 17, n. 1, p. 63-73, 2007.

MEEGALLA, S. K.; PLÖSSL, K.; KUNG, M. P.; CHUMPRADIT, S.; STEVENSON, D. A.; KUSHNER, S. A.; MCELGIN, W. T.; MOZLEY, P. D.; KUNG, H. F. Synthesis and characterization of technetium-99m-labeled tropanes as dopamine transporter-imaging agents. **J Med Chem**, v. 40, n. 1, p. 9-17, 1997.

MOLINA, B. S.; PELHAM, W. E. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. **J Abnorm Psychol**, v. 112, n. 3, p. 497-507, 2003.

MOLINA, B. S.; PELHAM, W. E.; GNAGY, E. M.; THOMPSON, A. L.; MARSHAL, M. P. Attention-deficit/hyperactivity disorder risk for heavy drinking and alcohol use disorder is age specific. **Alcohol Clin Exp Res**, v. 31, n. 4, p. 643-654, 2007.

MURPHY, K. R.; BARKLEY, R. A.; BUSH, T. Young adults with attention deficit hyperactivity disorder: subtype differences in comorbidity, educational, and clinical history. **J Nerv Ment Dis**, v. 190, n. 3, p. 147-157, 2002.

MUSSER, C. J.; AHMANN, F. W.; MUNDT, P. Stimulant use and the potential for abuse in Wisconsin as reported by school administrators and longitudinally followed children. **J Dev Behav Pediatr**, v. 19, p. 187-192, 1998.

NIGG, J. T.; CASEY, B. J. An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. **Dev Psychopathol**, v. 17, p. 785-806, 2005.

ORGANIZAÇÃO DAS NAÇÕES UNIDAS PARA EDUCAÇÃO, CIÊNCIA E TECNOLOGIA (UNESCO). Jornal Zero Hora, Porto Alegre, p. 31, 12/11/2002.

POLANCZYK, G.; HORTA, B.; LIMA, M.; BIEDERMAN, J.; ROHDE, L. A. The worldwide prevalence of ADHD. A systematic review and meta-regression analysis. **Am J Psychiatry**, v. 164, n. 6, p. 942-948, 2007.

RIGGS, P. D.; HALL, S. K.; MIKULICH-GILBERTSON, S. K.; LOHMAN, M.; KAYSER, A. A randomized controlled trial of pemoline for attention-deficit/hyperactivity disorder in substance-abusing adolescents. **J Am Acad Child Adolesc Psychiatry**, v. 43, n. 4, p. 420-429, 2004.

RIGGS, P. D.; LEON, S. L.; MIKULICH, S. K.; POTTLE, L. C. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. **J Am Acad Child Adolesc Psychiatry**, v. 37, n. 12, p. 1271-1278, 1998.

RODRIGUEZ DE FONSECA, F.; DEL ARCO, I.; BERMUDEZ-SILVA, F. J.; BILBAO, A.; CIPPITELLI, A.; NAVARRO, M. The endocannabinoid system: physiology and pharmacology. **Alcohol Alcohol**, v. 40, n. 1, p. 2-14, 2005.

RUSH, C. R.; ESSMAN, W. D.; SIMPSON, C. A.; BAKER, R. W. Reinforcing and subject-rated effects of methylphenidate and d-amphetamine in non-drug-abusing humans. **J Clin Psychopharmacol**, v. 21, n. 3, p. 273-286, 2001.

SARTOR, C. E.; LYNSKEY, M. T.; HEATH, A. C.; JACOB, T.; TRUE, W. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. **Addiction**, v. 102, n. 2, p. 216-225, 2007.

SCHUBINER, H.; SAULES, K. K.; ARFKEN, C. L.; JOHANSON, C. E.; SCHUSTER, C. R.; LOCKHART, N.; EDWARDS, A.; DONLIN, J.; PIHLGREN, E. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. **Exp Clin Psychopharmacol**, v. 10, n. 3, p. 286-294, 2002.

SCHUBINER, H.; TZELEPIS, A.; MILBERGER, S.; LOCKHART, N.; KRUGER, M.; KELLEY, B. J.; SCHOENER, E. P. Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. **J Clin Psychiatry**, v. 61, n. 4, p. 244-251, 2000.

SCHWERI, M. M.; SKOLNICK, P.; RAFFERTY, M. F.; RICE, K. C.; JANOWSKY, A. J.; PAUL, S. M. [^{3}H]Threo (+/-)-methylphenidate binding to 3,4-dihydrophenylethylamine uptake sites in corpus striatum: correlation with the stimulant properties of ritalinic acid esters. **J Neurochem**, v. 45, p. 1062-1070, 1985.

SEIDMAN, L. J.; VALERA, E. M.; MAKRIS, N. Structural brain imaging of attention-deficit/hyperactivity disorder. **Biol Psychiatry**, v. 57, p. 1263-1272, 2005.

SHAO, C.; LI, Y.; JIANG, K.; ZHANG, D.; XU, Y.; LIN, L.; WANG, Q.; ZHAO, M.; JIN, L. Dopamine D4 receptor polymorphism modulates cue-elicited heroin craving in Chinese. **Psychopharmacology**, v. 186, n. 2, p. 185-190, 2006.

SOLHKHAH, R.; WILENS, T, E.; DALY, J.; PRINCE, J. B.; VAN PATTEN, S. L.; BIEDERMAN, J. Bupropion SR for the treatment of substance-abusing outpatient adolescents with attention-deficit/hyperactivity disorder and mood disorders. **J Child Adolesc Psychopharmacol**, v. 15, n. 5, p. 777-786, 2005.

SOMOZA, E. C.; WINHUSEN, T. M.; BRIDGE, T. P.; ROTROSEN, J. P.; VANDERBURG, D. G.; HARRER, J. M.; MEZINSKIS, J. P.; MONTGOMERY, M. A.; CIRAULO, D. A.; WULSIN, L. R.; BARRETT, J. A. An open-label pilot study of methylphenidate in the treatment of cocaine dependent patients with adult attention deficit/hyperactivity disorder. **J Addict Dis**, v. 23, n. 1, p. 77-92, 2004.

SOMOZA, E. C.; WINHUSEN, T. M.; BRIDGE, T. P.; ROTROSEN, J. P.; VANDERBURG, D. G.; HARRER, J. M.; MEZINSKIS, J. P.; MONTGOMERY, M. A.; CIRAULO, D. A.; WULSIN, L. R.; BARRETT, J. A. An open-label pilot study of methylphenidate in the treatment of cocaine dependent patients with adult attention deficit/hyperactivity disorder. **J Addict Dis**, v. 23, n. 1, p. 77-92, 2004.

SONUGA-BARKE, E. J. Psychological heterogeneity in AD/HD--a dual pathway model of behaviour and cognition. **Behav Brain Res**, v. 10, p. 29-36, 2002.

SPENCER, T. J.; BIEDERMAN, J.; CICCONE, P. E.; MADRAS, B. K.; DOUGHERTY, D. D.; BONAB, A. A.; LIVNI, E.; PARASRAMPURIA, D. A.; FISCHMAN, A. J. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. **Am J Psychiatry**, v. 163, n. 3, p. 387-395, 2006.

SPENCER, T. J.; BIEDERMAN, J.; MICK, E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. **Ambul Pediatr**, v. 7, suppl 1, p. 73-81. 2007.

SPENCER, T.; BIEDERMAN, J.; WILENS, T.; HARDING, M.; O´DONNELL, D.; GRIFFIN, S. e cols. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle**. J Am Acad Child Adolesc Psychiatry**, v. 35, n. 4, p. 409-428, 1996.

STANSFIELD, K. H.; KIRSTEIN, C. L. Neurochemical effects of cocaine in adolescence compared to adulthood. **Brain Res Dev Brain Res**, v. 6, n. 159(2), p. 119-125, 2005.

TAPERT, S. F.; BARATTA, M. V.; ABRANTES, A. M.; BROWN, S. A. Attention dysfunction predicts substance involvement in community youths. **J Am Acad Child Adolesc Psychiatry**, v. 41, n. 6, p. 680-686, 2002.

TARTER, R.E. Etiology of adolescent substance abuse: a developmental perspective. **Am J Addict.** 11:171-91, 2002.

TETER, C. J.; McCABE, S. E.; LAGRANGE, K.; CRANFORD, J. A.; BOYD, C. J. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. **Pharmacotherapy**, v. 26, n. 10, p. 1501-1510, 2006.

TODD, R. D.; HUANG, H.; SMALLEY, S. L.; NELSON, S. F.; WILLCUTT, E. G.; PENNINGTON, B. F.; SMITH, S. D.; FARAONE, S. V.; NEUMAN, R. J. Collaborative analysis of DRD4 and DAT genotypes in population-defined ADHD subtypes. **J Child Psychol Psychiatry**, v. 46, n. 10, p. 1067-1073, 2005.

TZAVARA, E. T.; LI, D. L.; MOUTSIMILLI, L.; BISOGNO, T.; DI MARZO, V.; PHEBUS, L. A.; NOMIKOS, G. G.; GIROS, B. Endocannabinoids activate transient receptor potential vanilloid 1 receptors to reduce hyperdopaminergia-related hyperactivity: therapeutic implications. **Biol Psychiatry**, v. 15, n. 59(6), p. 508-515, 2006.

VOLKOW, N. D. Stimulant medications: how to minimize their reinforcing effects? **Am J Psychiatry**, v. 163, n. 3, p. 359-361, 2006.

VOLKOW, N. D.; DING, Y. S.; FOWLER, J. S.; WANG, G. J.; LOGAN, J.; GATLEY, J. S.; DEWEY, S.; ASHBY, C.; LIEBERMANN, J.; HITZEMANN, R.; WOLF, A. P. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. **Arch Gen Psychiatry**, v. 52, n. 6, p. 456-463, 1995.

VOLKOW, N. D.; FOWLER, J. S.; WANG, G. J. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. **Neuropharmacology**, v. 47, suppl 1, p. 3-13, 2004.

WEISS, G.; HECHTMAN, L.; MILROY, T.; PERLMAN, T. Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. **J Am Acad Child Psychiatry**, v. 24, n. 2, p. 211-220, 1985.

WHITE, A. M.; JORDAN, J. D.; SCHROEDER, K. M.; ACHESON, S. K.; GEORGI, B. D.; SAULS, G.; ELLINGTON, R. R.; SWARTZWELDER, H. S. Predictors of relapse during treatment and treatment completion among marijuana-dependent adolescents in an intensive outpatient substance abuse program. **Subst Abus**, v. 25, n. 1, p.53-59, 2004.

WILENS, T. E.; FARAONE, S. V.; BIEDERMAN, J.; GUNAWARDENE, S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. **Pediatrics**, v. 111, n. 1, p. 179-85, 2003.

WILENS, T. E.; GIGNAC, M.; SWEZEY, A.; MONUTEAUX, M. C.; BIEDERMAN, J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. **J Am Acad Child Adolesc Psychiatry**, v. 45, n. 4, p. 408-414, 2006.

WILLIAMS, R. J.; GOODALE, L. A.; SHAY-FIDDLER, M. A.; GLOSTER, S. P.; CHANG, S. Y. Methylphenidate and dextroamphetamine abuse in substance-abusing adolescents. **Am J Addict**, v. 13, n. 4, p. 381-389, 2004.

ZARIN, D. A.; SUAREZ, A. P.; PINCUS, H. A.; KUPERSANIN, E.; ZITO, J. M. Clinical and treatment characteristics of children with attention-deficit/hyperactivity disorder in psychiatric practice. **J Am Acad Child Adolesc Psychiatry**, v. 37, p. 1262-1270, 1998.

ANEXOS

ANEXO 1

Attention-Deficit Hyperactivity Disorder and Substance Use Disorders

(In press, Child & Adolescent Psychiatric Clinics of North America)

Attention-Deficit Hyperactivity Disorder and Substance Use Disorders

Szobot, Claudia M[1] M.D. and Bukstein, Oscar[2] M.D

[1]Attention-Deficit/ Hyperactivity Disorder Outpatient Clinic, Hospital de Clínicas de Porto Alegre (HCPA), Federal University of Rio Grande do Sul (UFRGS), Brazil; Center for Drug and Alcohol Research HCPA, UFRGS. Correspondence: Programa de Déficit de Atenção/Hiperatividade (PRODAH), Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos, 2350, segundo andar, sala 2201A; phone/pax: 55 51 2101-8094. CEP 90035-003. Porto Alegre, Brasil. e-mail: **cmszobot@terra.com.br**

[2]Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, United States. Correspondence: e-mail: BuksteinOG@upmc.edu

Corresponding author for proofs and reprint: Dr. Claudia Szobot

Keywords: Attention-Deficit Hyperactivity Disorder, Substance Use Disorders, etiology, treatment, stimulant, adolescent.

Adolescent Substance Use Disorder (SUD) is a major mental health concern (1, 2) and one of the most prevalent disorders in adolescents (3). It is well known that SUD has a multivariate etiology, with the influence of both biological and environmental variables (4, 5). As a significant group of adults with SUD have an onset of their SUD diagnosis before the age 18 years (6), much attention has been given to the role of childhood psychopathology in the vulnerability to further SUD. Several studies have suggested ADHD as a risk factor to SUD, since: a) ADHD is usually overrepresented among adolescents with SUD (7, 8, 9); b) since ADHD onset is before age 7 years (10), this disorder usually is already present several years before drug experimentation.

Etiological Association

Theoretical and empirical reviews of the development of SUDs point to the early appearance of behavioral undercontrol characteristics, including the core symptoms of ADHD (inattention, impulsivity, and hyperactivity) in children prior to the onset of substance use (11, 12, 13). In the Dunedin Health and Development Study, it was reported that behavioral undercontrol at age 3 (impulsivity, impersistence, and difficulty sitting still) predicted alcohol dependence at age 21 (14). In the Montreal Longitudinal Study, novelty-seeking at ages 6 and 10 (reported by teachers as restless, runs/jumps and doesn't keep still, squirmy and fidgety) predicted drug use and cigarette smoking in adolescence (15). Also, in another study, ADHD symptoms and poor response inhibition were related to adolescent problem drinking (16).

Recent prospective longitudinal studies of substance use and SUD in children with ADHD support the hypothesis that children with Diagnostic and Statitistical Manual of Mental Disorders (DSM)-III-R or DSM-IV ADHD are at risk for adverse substance use

outcomes. Two independent samples of adolescents followed from childhood (when they were diagnosed with ADHD) showed an increased risk for having used illicit drugs in the past 6 months, heavy marijuana use, and heavy cigarette use (17) heavy drinking (17, 18), Alcohol Use Disorder (AUD) symptoms (17) and AUD (18), in the mid-to-late teens.

However, up to now, there is no agreement in the literature whether ADHD is an independent risk factor for SUD when results consider the presence of Conduct Disorder (CD), a well known risk factor for SUD (19). CD is highly prevalent among adolescents with ADHD (20, 21) and some evidence suggest that only those ADHD youths with comorbid CD would be at higher risk. Interestingly, studies trying to disentangle the role of ADHD on the development of SUD have contradictory results. In Table 1, we summarize the main studies on this topic:

PLEASE INSERT TABLE 1 ABOUT HERE

Differences in methodology may account for the discordant results among the studies. Such differences include, for example, different definitions of drug problem, characteristics of the samples (e.g., age, origin of the sample - clinical or community) and history of ADHD treatment. If ADHD pharmacotherapy is protective for the development of substance use and SUD in adolescents as suggested by Biederman (1999) (34) and Wilens (2003) (35), an effect of ADHD on higher SUD risk may be reduced, and the effect of CD would be more evident in samples including treated subjects for ADHD.

Considering a multivariate etiological model of adolescent ADHD, it seems reasonable to consider that untreated ADHD could be an independent risk factor for further SUD. Different lines of evidence support this possibility.

Developmental perspective

From a developmental perspective for adolescent psychopathology, ADHD has an earlier age of onset than either CD or SUD. Some of the ADHD-associated impairments (such as peer rejection and academic problems) through childhood and adolescence are consistently mentioned in the literature as enhancing the adolescent SUD liability (36). Since CD onset usually occurs some years after ADHD onset, an untreated ADHD child may manifest several impairments, clearly associated with higher risk SUD, prior to a diagnosis of CD or antisocial behavior.

Neurobiological perspective

From a neurobiological perspective, it is also possible to consider ADHD as an early antecedent of SUD. Children with ADHD have dysfunctions in the dopaminergic circuits, mostly in basal ganglia and frontal cortex (37), with defects in executive function (38) and in the reward system (39). The dopamine system has long been implicated also in alcohol/illicit drugs dependence addiction (40, 41, 42, 43). For example, dopaminergic system genes have been involved in both ADHD (44, 45) and drug problems (46, 47, 48, 49).

Dopamine-regulated areas, such as the basal ganglia and frontal areas, are affected in both ADHD and SUD subjects (50). Executive (51) and reward system functions (50) have a strong influence on SUD liability. Thus, children with ADHD have cognitive dysfunctions that may impair them in high-risk drug use situations, like their tendency in overestimating their competence (52, 53) and in sustaining a behavior despite negative consequences (54). An adolescent with ADHD might have more difficulties to accurately evaluate the negative consequences of drug use or a high risk situation for drug use, which in an important mechanism in order to avoid drug use. If the adolescent realizes that drug use is resulting in negative consequences, such as family problems, they might have more difficulty in changing

to a healthier behavior, due to their impaired cognitive flexibility. Furthermore, ADHD and SUD may have similar dysfunctions in the brain reward system (RS). The RS is associated with motivation, salience of a stimulus (55) and delay capacity (39). As a result, a youth with ADHD may choose a more immediate but ultimately worst reward rather than delayed gratification for future benefit(s). Impulsive behavior and choices are associated with drug use. Subjects with SUD may decide on choices with high immediate gains in spite of higher future losses (56).

Self-medication

Some ADHD symptoms might be attenuated with drug use. So, after drug experimentation, some adolescents may feel or behave better, which may further reinforce drug use. For example, the acute use of nicotine, a substance with stimulant properties, is associated with an improvement in some cognitive functions (57). As a consequence, individuals with ADHD, after nicotine experimentation, might feel a cognitive improvement, leading to repeated use. Not surprisingly, individuals with ADHD are at higher risk for nicotine regular use (58, 59). In a number of prospective longitudinal studies, childhood ADHD has predicted an increased risk of cigarette smoking by adolescence and by young adulthood. These studies include children ascertained in clinic samples (17, 60) and in a community sample in which most children were diagnosed as hyperactive by community practitioners in addition to research criteria (61).

In sum, more studies are needed in order to better elucidate the possibility of an independent effect of ADHD on the etiology of SUD. These studies should, preferable, adjust the results for the effect of ADHD treatment and for the presence of CD. Also, it would be important to have enough sample size to estimate the effect of both attention and hyperactivity/ impulsivity dimensions of ADHD on further SUD. While the debate is still

open, it is reasonable to pay attention to ADHD impairments that might make a link with SUD, such as poor academic performance, or impulsive choices. Also, clinicians should be aware of ADHD symptoms that can be initially attenuated with first drug contacts (e.g., impulsivity and cannabis; inattention and nicotine).

Pharmacological treatment

As already described, there is a significant association between ADHD and SUD in adolescents, regardless of the existence or not of direct cause-effect relation or whether this relationship is mediated by the presence of CD. The comorbidity is clinically relevant, since ADHD is associated with a worse SUD prognosis, for different categories of substances. There is evidence for an association between childhood ADHD and smoking cessation treatment failure (62), for earlier and more frequent alcohol relapses (63), and for a lower likelihood of cannabis treatment completion in adolescents (64). Despite the clinical relevance of ADHD treatment in adolescents with current SUD, few treatment studies have been conducted in this comorbid population. Due to the absence of psychosocial treatment studies, we present a summary of the literature on pharmacological studies.

Stimulants

Several evidence-based guidelines suggest that stimulants (e.g., methylphenidate - MPH) should be the first option for treatment of ADHD (see, for instance, reference 65), but ADHD treatment studies typically exclude individuals with drug use/misuse or SUD. Since ADHD (66), MPH (67) and most abused drugs (50, 68, 69, 70) are associated with dysfunctions and/or actions on dopaminergic system, MPH clinical and neurobiological effects might not necessarily be generalized to this dually-diagnosed population. Cocaine, for

example, increases dopamine (DA) by blocking striatal dopamine transporter (DAT) (71), the same target of MPH. Moreover, there is a body of evidence describing that cannabis, the most abused illicit drug worldwide (73) affects dopamine regulation (68, 70, 73). Thus, MPH clinical effect might not be the same in the context of acute or chronic drug exposure, highlighting the need of treatment protocols derived from studies based on ADHD/SUD samples, and not just on ADHD or ADHD plus other comorbidities.

The lack of studies with stimulants in adolescents with ADHD/SUD might reflect a concern regarding its abuse potential, already described in human studies (74, 75). However, there is evidence suggesting that childhood treatment with MPH is associated to a protection for SUD development. A longitudinal study of children with ADHD treated with stimulants and followed for approximately 13 years found no evidence that stimulant treatment leaded to an increased risk of substance experimentation, use, abuse or dependence by adulthood (76). In a meta-analytic review of the literature, the pooled estimate of the odds ratio indicated a 1.9-fold reduction in risk for SUD in youths who received pharmacotherapy for ADHD (35). However, more recent reports from a large prospective study of ADHD youths found that while a history of treatment with a psychostimulant had no effect on substance use in ADHD adolescents, a history of psychostimulant treatment appeared to be associated with increased marijuana use, cigarette use, and binge drinking in young adults (77).

Interestingly, we were not able to find many treatment studies with stimulants, independent of the formulation, for adolescents with ADHD/SUD. In a randomized, double-blind, placebo-controlled trial of the stimulant pemoline (discontinued in the United States in October 2005 due to liver toxicity) in adolescents with comorbid ADHD and SUD, the stimulant medication was shown to improve ADHD symptoms but to have little, if any, effect on substance use (78). Recently, the effectiveness of a long-acting formulation of

methylphenidate (MPH-SODAS) on ADHD symptoms was evaluated in an outpatient sample of adolescents with ADHD and illicit SUD in a crossover, placebo controlled trial. In this study, subjects (mostly cannabis users) had a significantly higher reduction in the Swanson, Nolan and Pelham Scale – version IV (SNAP-IV) and the Clinical Global Impression Scale (CGI) scores ($p<0.001$ for all analyses) during MPH-SODAS treatment when compared to placebo. There was no significant effect over drug use and MPH-SODAS was well-tolerated, but it was associated with more severe appetite reduction than placebo ($p<0.001$) (Szobot et al., *submitted*).

The few available Randomized Clinical Trials (RCTs) were conducted only with adults and some did not find a superior effect of MPH over placebo (79, 80, 81). Schubiner et al (82) reported significant reductions in ADHD symptoms ($p = .0039$) and a decline in cocaine craving with MPH use when compared to placebo, although there was no difference in cocaine use. However it is important to note that approximately 47% of the sample dropped out from the study. These findings may not necessarily be translated to adolescents, since there are reports of different MPH (83) and drug responses between adults and adolescents (84, 85, 86).

Bupropion

Although bupropion is not a first line ADHD medication (65), it is the most studied medication in adolescents with ADHD/SUD, probably because it is considered safer in terms of misuse/abuse. Bupropion appears to have a low abuse potential on physiological measures compared with dextroamphetamine (87). The approval by the Food and Drug Administration (FDA) for the use of bupropion for smoking cessation and its efficacy in controlled clinical trials (88) suggest the potential value of this agent for addictive disorders. However, only open trials with this medication were conducted in adolescents with ADHD plus SUD up to

now. Riggs et al (89) evaluated bupropion effects on 13 adolescents with ADHD/SUD/CD in a residential program. In this 5-week open trial, there was a significant reduction in scores of ADHD outcome measures. Solhkhah et al. (90) evaluated effects of bupropion SR over ADHD symptoms in 14 adolescents with ADHD/SUD associated with mood disorder in a 6-month open trial. The authors reported a significant reduction in drug use and ADHD symptoms. We were not able to find controlled studies with bupropion in adolescents with ADHD/SUD.

Other Non-Stimulants

Due to the absence of evidence regarding abuse potential, atomoxetine was not listed as a scheduled drug by the Drug Enforcement Agency (DEA). Further evidence of atomoxetine's lack of abuse potential is provided by a finding of lack of increase extra cellular dopamine in the nucleus acumbens of rats (91). The nucleus acumbens is involved in the reward aspects of drug use, which appears to be mediated through dopamine. Heil (2002) (92) reported that atomoxetine did not produce subjective effects similar to methylphenidate, thus suggesting it's absence of abuse liability. However, we were not able to find atomoxetine studies' on adolescents with ADHD + SUD.

Modafinil, marketed for the treatment of daytime sleepiness in narcolepsy, has effects on glutamate and GABA neurotransmitter systems that may oppose some effects of chronic cocaine administration, as well as an alerting effect that may ameliorate some of the vegetative symptoms of cocaine withdrawal and may blunt cocaine euphoria (93). Moreover, dose-related effects on prepotent inhibition in normal volunteers, as well as patients with ADHD, suggests a positive effect of modafinil in reducing impulsive responding (94, 95). A double-blind, placebo-controlled trial in 62 cocaine-dependent men and women reported increased cocaine abstinence in the modafinil group (96). Trials in children and adolescents

with ADHD show improvement in ADHD symptoms for modafinil over placebo while demonstrating its safety and tolerability in doses up to 425 mg/day (97, 98).

Stimulant abuse/diversion

In order to try to consider an algorithm for pharmacological treatment of ADHD, stimulant abuse/diversion data should be considered. It is well known that adolescents with SUD can divert or misuse stimulants (99, 100), creating an intriguing scenario for ADHD pharmacological treatment in youths already with drug problems. The misuse of stimulants as "study drugs" (101) is not uncommon on college campuses. A recent Web-based survey found a 6 % past-year prevalence and a lifetime prevalence of 8% of stimulant misuse in 4580 college students (75% used amphetamines, 25% methylphenidate) (102) A mail-in survey of 11,000 college students at 119 institutions reported a 4% past-year prevalence for non-medical use of stimulants (7% lifetime) (103). Most undergraduates (60%) who reported MPH misuse in a cohort at one college (prevalence: 5.4% of 9,000 surveyed) reported that stimulants "help me concentrate" and 40% said stimulant use "helps increase my awareness", and another 40% reported that use of immediate-release stimulants "gives me a high" (104).

Recently, Wilens (2006) (105) evaluated the characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. Regarding to immediate-release methylphenidate (the only formulation of MPH reported in the sample), 11% of the subjects (all with an additional diagnosis of CD, SUD or both) sold the medication for others, and 22% misused the medication (from whom 83% had also CD, SUD or both). Thus, the presence of comorbid CD and/or SUD was a significant risk factor for misuse and/or diversion.

The route of administration and the rates of onset and offset in the brain play critical roles in determining the risk of chemical dependency (71). A recent brain imaging study

supports that the abuse potential of sustained-release formulations may be less than with immediate-release formulations (67). These findings suggest that the newer, longer-acting stimulants such as extended-release methylphenidate, dexmethylphenidate extended release, lisdexamphetamine, or the extended-release formulation of mixed amphetamine salts may have a lower abuse/misuse/diversion potential than immediate-release preparations of psychostimulants. In addition, once a day medications may be easier to monitor compliance and possible diversion. However, up to now, there is no empiric data, derived from adolescents, to support this possibility.

Conclusions

While we do not have enough RCTs in adolescents with ADHD plus SUD describing treatment effects over ADHD symptoms, drug use, and medication abuse/diversion, clinicians are challenged with intriguing issues, such as: a) should they prescribe bupropion, avoiding concerns about abuse/diversion but offering a medication with smaller effect size for ADHD than stimulants? This is intriguing, since, as already reported, there is evidence that untreated ADHD is associated with a worse SUD prognosis; b) should they prescribe stimulants, taking the risk of abuse/diversion?

Up to now, there is not enough data in the adolescent literature to support a treatment algorithm for adolescents with ADHD plus SUD. Given concerns about abuse/misuse/diversion, the mixed literature on the effectiveness of treating ADHD in SUD patients does not support specific drugs, time for initiation and length of therapy. In adolescents, open-label trials with bupropion and clinical experience are providing some guidance. Some investigators have proposed that non-stimulant agents (atomoxetine), and antidepressants (bupropion) are preferable to stimulants in adolescents with ADHD and active SUD symptoms/behaviors. For those with poor response to these agents, stable treatment for

SUD, or merely a history of SUD or recreational/experimental substance use (assuming non-amphetamine SUD), the use of extended-release or longer acting stimulants with lower abuse liability and diversion potential is recommended. However, it is important to note that there is no evidence-based information to support this perspective.

In the absence of clear evidence of ongoing diversion (misuse and reselling) or high-risk situations (e.g., family member with an active SUD, antisocial personality disorder in the patient or family members), the threat of or potential for diversion should not be the sole reason for withholding or not using stimulant medications. Rather, the clinician should always evaluate risk factors for diversion and set up a clear plan of control and administration of the stimulant (or other) medication. Clinicians should monitor prescriptions carefully with high suspicion directed toward early requests for refills or lost prescriptions. The treating physician must require frequent follow-up for all ADHD-SUD patients; questionnaires, objective toxicology screens, and contingency plans are suggested. At last, despite variable improvements in ADHD symptoms, the existing studies rarely produced significant improvements in substance use. Therefore, specific treatment for an active SUD is critical (1).

Synopsis

Attention-Deficit Hyperactivity Disorder (ADHD) is highly prevalent among adolescents with Substance Use Disorder (SUD). Several lines of evidence, although not conclusive, suggest that ADHD might have an independent effect on SUD liability. However, it is still to be determined whether this association is mediated by Conduct Disorder. If ADHD would be an independent risk factor, this might have preventive implications. Since ADHD begins in early childhood, before the onset of SUD, these at-risk children can be

identified and targeted for early and ongoing intervention to help preventing the onset of SUD. Regarding to the treatment of adolescents with ADHD plus SUD, few studies have evaluated pharmacological interventions in this population. Up to now, there is no clear algorithm for the pharmacological treatment of adolescents with ADHD plus SUD. If a stimulant medication is prescribed, there is an important concern regarding its potential of abuse/misuse/diversion in this specific population. Medications such as methylphenidate extended release and atomoxetine seem very promising for this dually diagnosed population. In addition, more studies are needed to identify optimal psychosocial treatment approaches for adolescents with both ADHD and SUD.

Conflict of interest: Dr. Szobot: Janssen-Cilag speaker's bureau; travel suppor by Novartis. Dr.Bukstein: Shire Pharmcueticals – consultant, research support, and speaker's bureau; McNeil pediatrics – speaker's bureau, consultant; Eli Lilly – research support; Novartis – speaker's bureau

References

1. Bukstein OG, Bernet W, Arnold V, et al. Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. J Am Acad Child Adolesc Psychiatry 2005; 44:609-21.

2. Galduroz JC, Noto AR, Nappo SA, et al. Household survey on drug abuse in Brazil: study involving the 107 major cities of the country--2001. Addict Behav 2005; 30:545-56.

3. Costello EJ, Mustillo S, Erkanli A, et al. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry 2003;60(8):837-44.

4. Kendler KS, Jacobson KC, Prescott CA, et al. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. Am J Psychiatry 2003;160 (4):687-95.

5. Callas PW, Flynn BS, Worden JK. Potentially modifiable psychosocial factors associated with alcohol use during early adolescence. Addict Behav. 2004; 29(8):1503-15.

6. Kim-Cohen J, Caspi A, Moffitt TE, et al. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry 2003; 60:709-17.

7. Horner BR, Scheibe KE. Prevalence and implications of attention-deficit hyperactivity disorder among adolescents in treatment for substance abuse. J Am Acad Child Adolesc Psychiatry 1997;36(1):30-6.

8. DeMilio L. Psychiatric syndromes in adolescent substance abusers. Am J Psychiatry 1989; 146(9):1212-4.

9. Szobot CM, Rohde LA, Bukstein O, et al. Is attention-deficit/hyperactivity disorder associated with illicit substance use disorders in male adolescents? A community-based case-control study. Addiction. 2007;102(7):1122-1130.

10. American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders,* (4th edition). Washington, DC, American Psychiatric Association.

11. Sher KJ. (1991). Children of alcoholics: A critical appraisal of theory and research. Chicago: University of Chicago Press.

12. Zucker RA, Gomberg ES. Etiology of alcoholism reconsidered. The case for a biopsychosocial process. Am Psychol 1986;41(7):783-93.

13. Zucker RA. (2006). Alcohol use and the alcohol use disorders: A developmental biopsychosocial systems formulation covering the life course. In (Eds.) D. Cicchetti & D.J. Cohen (Eds.) Developmental Psychopathology, Volume 3, Risk, Disorder, and Adaptation, 2nd Edition, pp 620-656, Hoboken, NJ: Wiley & Sons.

14. Caspi A, Moffitt TE, Newman DL, et al. Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. Archives of General Psychiatry 1996; 53:1033-1039.

15. Masse LC, Tremblay RE. Behavior of boys in kindergarten and the onset of substance use during adolescence. Archives of General Psychiatry 1997; 54:62-68.

16. Nigg JT, Wong MM, Martel MM, et al. Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. Journal of the American Academy of Child and Adolescent Psychiatry 2006; 45(4):468-475.

17. Molina B, Pelham WE. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. Journal of Abnormal Psychology 2003; 112(3):497-507.

18. Molina BSG, Pelham WE, Gnagy EM, et al. ADHD risk for heavy drinking and alcohol use disorder is age-specific. Alcoholism: Clinical and Experimental Research 2007; 31(4):643-654.

19. Myers MG, Stewart DG, Brown SA. Progression from conduct disorder to antisocial personality disorder following treatment for adolescent substance abuse. Am J Psychiatry 1998; 155(4):479-85.

20. Clark DB, Cornelius JR, Kirisci L, et al. Childhood risk categories for adolescent substance involvement: a general liability typology. Drug Alcohol Depend 2005; 77:13-21.

21. Biederman J, Wilens T, Mick E, et al. Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 1997; 36:21-9.

22. Carroll KM, Rounsaville BJ. History and significance of childhood attention deficit disorder in treatment-seeking cocaine abusers. Compr Psychiatry 1993; 34(2):75-82.

23. Kuperman S, Schlosser SS, Kramer JR, et al. Developmental sequence from disruptive behavior diagnosis to adolescent alcohol dependence. Am J Psychiatry 2001; 158(12):2022-6.

24. Biederman J, Wilens T, Mick E, et al. Psychoactive substance use disorders in adults with attention deficit hyperactivity disorder (ADHD): effects of ADHD and psychiatric comorbidity. Am J Psychiatry 1995; 152(11):1652-8.

25. Biederman J, Wilens TE, Mick E, et al. Does attention-deficit hyperactivity disorder impact the developmental course of drug and alcohol abuse and dependence? Biol Psychiatry 1998; 44(4):269-73.

26. Murphy KR, Barkley RA, Bush T. Young adults with attention deficit hyperactivity disorder: subtype differences in comorbidity, educational, and clinical history. J Nerv Ment Dis 2002; 190(3):147-57.

27. Weiss G, Hechtman L, Milroy T, et al. Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. J Am Acad Child Psychiatry 1985; 24(2):211-20.

28. Biederman J, Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol Med 2006; 36(2):167-79.

29. August GJ, Winters KC, Realmuto GM, et al. Prospective study of adolescent drug use among community samples of ADHD and non-ADHD participants. J Am Acad Child Adolesc Psychiatry 2006; 45(7):824-32.

30. Disney ER, Elkins IJ, McGue M, et al. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. Am J Psychiatry 1999; 156:1515-21.

31. Tapert SF, Baratta MV, Abrantes AM, et al. Attention dysfunction predicts substance involvement in community youths. J Am Acad Child Adolesc Psychiatry 2002; 41(6):680-6.

32. Gau SS, Chong MY, Yang P, et al. Psychiatric and psychosocial predictors of substance use disorders among adolescents: longitudinal study. Br J Psychiatry 2007;190:42-8.

33. Fergusson DM, Horwood LJ, Ridder EM. Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. Drug Alcohol Depend. 2007 Apr;88 Suppl 1:S14-26

34. Biederman J, Wilens T, Mick E, et al. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. Pediatrics. 1999;104(2):e20.

35. Wilens TE, Faraone SV, Biederman J, et al. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 2003; 111:179-85.

36. Tarter RE. Etiology of adolescent substance abuse: a developmental perspective. Am J Addict 2002; 11:171-91.

37. Seidman LJ, Valera EM, Makris N. Structural brain imaging of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005; 57:1263-72.

38. Fischer M, Barkley RA, Smallish L, et al. Executive functioning in hyperactive children as young adults: attention, inhibition, response perseveration, and the impact of comorbidity. Dev Neuropsychol 2005; 27:107-33.

39. Sonuga-Barke EJ. Psychological heterogeneity in AD/HD--a dual pathway model of behaviour and cognition. Behav Brain Res 2002; 10:29-36.

40. Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. Science 1988; 242:715-723.

41. Volkow ND, Wang GJ, Fowler JS, et al. Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry 2005; 57(11):1410-1415.

42. Volkow ND, Wang GJ, Begleiter H, et al. High levels of Dopamine D2 receptors in unaffected members of alcoholic famililes: Possible protective factors. Archives of General Psychiatry 2006; 63(9):999-1008.

43. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychological Review 1987; 94:469-492.

44. Cook EH, Stein MA, Ellison T, et al. Attention-deficit hyperactivity disorder and whole-blood serotonin levels - effects of comorbidity. Psychiatry Research 1995; 57(1):13-20.

45. LaHoste GJ, Swanson JM, Wigal SB, et al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry 1996; 1:121-124.

46. Goldman D. (1993). Genetic transmission. In M. Galanter (Ed.), Alcoholism (Vol. 11, pp. 232-244). New York: Plenum.

47. Robinson TE, Berridge KC. The neural basis of drug craving: An incentive-sensitization theory of addiction. Brain Research Review 1993; 18:247-291.

48. Pato CN, Macciardi F, Pato MT, et al. Review of the putative association of dopamine D2 receptor and alcoholism: A meta-analysis. American Journal of Medical Genetics 1993; 48:78-82.

49. Persico AM, Uhl GR. (1997). Polymorphisms of the D2 dopamine receptor gene in polysubstance abusers. In K. Blum and E. P. Noble (Ed.) Handbook of psychiatric genetics, Boca Raton, FL: CRC Press, Inc. PP 353-366.

50. Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology 2004; 47 3-13.

51. Tarter RE, Kirisci L, Mezzich A, et al. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. Am J Psychiatry 2003; 160:1078-85.

52. Gerdes AC, Hoza B, Pelham WE. Attention-deficit/hyperactivity disordered boys' relationships with their mothers and fathers: child, mother, and father perceptions. Dev Psychopathol 2003; 15:363-82.

53. Hoza B, Gerdes AC, Hinshaw SP, et al. Self-perceptions of competence in children with ADHD and comparison children. Journal of Consulting and Clinical Psychology 2004; 72(3):382-391.

54. Nigg JT, Casey BJ. An integrative theory of attention-deficit/ hyperactivity disorder based on the cognitive and affective neurosciences. Dev Psychopathol 2005; 17:785-806.

55. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005; 162:1403-13.

56. Bechara A, Martin EM. Impaired decision-making related to working memory deficits in individuals with substance addictions. Neuropsychology 2004; 18:152-62.

57. Weiss S, Nosten-Bertrand M, McIntosh JM, et al. Nicotine Improves Cognitive Deficits of Dopamine Transporter Knockout Mice without Long-Term Tolerance. Neuropsychopharmacology 2007 Mar 21.

58. Kollins SH, McClernon FJ, Fuemmeler BF. Association between smoking and attention-deficit/hyperactivity disorder symptoms in a population-based sample of young adults. Arch Gen Psychiatry 2005;62(10):1142-7.

59. Sartor CE, Lynskey MT, Heath AC, et al. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. Addiction 2007; 102(2):216-25.

60. Burke JD, Loeber R, Lahey BB. Which aspects of ADHD are associated with tobacco use in early adolescence? Journal of Child Psychology and Psychiatry 2001; 42: 493-502.

61. Lambert NM, Hartsough CS. Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. J Learn Disabil 1998;31(6):533-44

62. Humfleet GL, Prochaska JJ, Mengis M, et al. Preliminary evidence of the association between the history of childhood attention-deficit/hyperactivity disorder and smoking treatment failure. Nicotine Tob Res 2005 Jun;7(3):453-60.

63. Ercan ES, Coskunol H, Varan A, et al. Childhood attention deficit/hyperactivity disorder and alcohol dependence: a 1-year follow-up. Alcohol Alcohol 2003; 38(4):352-6.

64. White AM, Jordan JD, Schroeder KM, et al. Predictors of relapse during treatment and treatment completion among marijuana-dependent adolescents in an intensive outpatient substance abuse program. Subst Abus 2004; 25(1):53-9.

65. Pliszka SR, Crismon ML, Hughes CW, et al. Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of

attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2006;45(6):642-57.

66. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. Ambul Pediatr. 2007;7(1 Suppl):73-81.

67. Spencer TJ, Biederman J, Ciccone PE, et al. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry 2006;163(3):387-95.

68. Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, et al. The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol. 2005;40(1):2-14.

69. Koob GF. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. Addiction 2006;101 Suppl 1:23-30.

70. Tzavara ET, Li DL, Moutsimilli L, et al. Endocannabinoids activate transient receptor potential vanilloid 1 receptors to reduce hyperdopaminergia-related hyperactivity: therapeutic implications. Biol Psychiatry 2006;59(6):508-15.

71. Volkow ND, Ding YS, Fowler JS, et al. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry 1995;52(6):456-63.

72. World Health Organization (WHO): available at http://www.who.int/substance_abuse/facts/cannabis/en/index.html (assessed January 08, 2006).

73. Price DA, Owens WA, Gould GG, et al. CB(1)-independent inhibition of dopamine transporter activity by cannabinoids in mouse dorsal striatum. J Neurochem 2007;101(2):389-96.

74. Rush CR, Essman WD, Simpson CA, et al. Reinforcing and subject-rated effects of methylphenidate and d-amphetamine in non-drug-abusing humans. J Clin Psychopharmacol 2001;21(3):273-86.

75. Stoops WW, Lile JA, Fillmore MT, et al. Reinforcing effects of methylphenidate: influence of dose and behavioral demands following drug administration. Psychopharmacology (Berl) 2005;177(3):349-55.

76. Barkley RA, Fischer M, Smallish L, et al. Does the treatment of attention-deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. Pediatrics 2003;111(1):97-109.

77. Molina BSG, Marshal MP, Pelham WE, et al. Coping skills and parent support mediate the association between childhood ADHD and adolescent cigarette use. Journal of Pediatric Psychology 2005; 30(4):345-357.

78. Riggs PD, Hall SK, Mikulich-Gilbertson SK, et al. A randomized controlled trial of pemoline for attention-deficit/hyperactivity disorder in substance-abusing adolescents. J Am Acad Child Adolesc Psychiatry. 2004;43(4):420-429

79. Carpentier PJ, de Jong CA, Dijkstra BA, et al. A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. Addiction. 2005; 100(12):1868-74.

80. Levin FR, Evans SM, Brooks DJ, et al. Treatment of cocaine dependent treatment seekers with adult ADHD: Double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend. 2007; 87(1):20-9.

81. Levin FR, Evans SM, Brooks DJ, et al. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug Alcohol Depend. 2006; 81(2):137-48.

82. Schubiner H, Saules KK, Arfken CL, et al. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Exp Clin Psychopharmacol 2002; 10(3):286-94.

83. Kuperman S, Perry PJ, Gaffney GR, et al. Bupropion SR vs. methylphenidate vs. placebo for attention deficit hyperactivity disorder in adults. Ann Clin Psychiatry. 2001; 13(3):129-34.

84. Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry 2003; 160(6):1041-52.

85. Stansfield KH, Kirstein CL. Neurochemical effects of cocaine in adolescence compared to adulthood. Brain Res Dev Brain Res 2005;159(2):119-25.

86. Badanich KA, Adler KJ, Kirstein CL. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. Eur J Pharmacol. 2006; 550(1-3):95-106.

87. Griffith JD, Carranza J, Griffith C, et al. Bupropion: clinical essay for amphetamine-like potential. J Clin Psychiatry 1983; 44:206-208.

88. Goldstein MG. Bupropion sustained release and smoking cessation. J Clin Psychiatry. 1998 ; 59:66-72.

89. Riggs PD, Leon SL, Mikulich SK, et al. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry 1998; 37(12):1271-8.

90. Solhkhah R, Wilens TE, Daly J, et al. Bupropion SR for the treatment of substance-abusing outpatient adolescents with attention-deficit/hyperactivity disorder and mood disorders. J Child Adolesc Psychopharmacol 2005; 15(5):777-86.

91. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy inattention deficit/hyperactivity disorder. Neuropsychopharmacology 2002; 27:699-711.

92. Heil SH, Holmes HW, Bickel WK, et al. Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users. Drug Alcohol Depend 2002; 67(2), 149-156.

93. Dackis CA, Lynch KG, Yu E, et al. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. Drug Alcohol Depend 2003;70(1):29-37

94. Turner DC, Robbins TW, Clark L, et al. Cognitive enhancing effects of modafinil in healthy volunteers. Psychopharmacology 2003;165:260–269.

95. Turner DC, Clark L, Dowson J, et al. Modafinil improves cognition and response inhibition in adult attention deficit/hyperactivity disorder. Biol Psychiatry 2004; 55:1031–1040.

96. Dackis CA, Kampman KM, Lynch KG, et al. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. Neuropsychopharmacology *2005;* 30:205–211.

97. Rugino TA, Copley TC. Effects of modafinil in children with Attention-Deficit/Hyperactivity Disorder: An open-label study. J Am Acad Child Adolesc Psychiatry 2001; 40(2):230-235.

98. Biederman, J, Swanson JM, Wigal SB, et al. Comparison of Once-Daily and Divided Doses of Modafinil in Children With Attention-Deficit/Hyperactivity Disorder: A Randomized, Double-Blind, and Placebo-Controlled Study. Journal of Clinical Psychiatry 2006; 67(5): 727-735.

99. Gordon SM, Tulak F, Troncale J. Prevalence and characteristics of adolescents patients with co-occurring ADHD and substance dependence. J Addict Dis. 2004;23(4):31-40.

100. Williams RJ, Goodale LA, Shay-Fiddler MA, et al. Methylphenidate and dextroamphetamine abuse in substance-abusing adolescents. Am J Addict. 2004;13(4):381-9.

101. Sussman S, Pentz MA, Spruijt-Metz D, et al. Misuse of "study drugs:" prevalence, consequences, and implications for policy. Subst Abuse Treat Prev Policy 2006; Jun 9;1:15.

102. Teter CJ, McCabe SE, LaGrange K, et al. Illicit use of specific prescription stimulants among college students: prevalence, motives, and routes of administration. Pharmacotherapy 2006;26(10):1501-10.

103. McCabe SE, Knight JR, Teter CJ, et al. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. Addiction 2005; 100:96-106.

104. Teter CJ, McCabe SE, Cranford JA, et al. Prevalence and motives for illicit use of prescription stimulants in an undergraduate student sample. J Am Coll Health 2005;53:253-262.

105. Wilens TE, Gignac M, Swezey A, et al. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. J Am Acad Child Adolesc Psychiatry 2006;45(4):408-14.

Table 1 - Studies on the association of Attention Deficit/Hyperactivity Disorder and SUD

Author	Study Design and Sample	Main results
A) Sample: individuals with SUD		
Carrol and Rousanville, 1993 (22)	Prevalence; clinic; 298 adults; cocaine users	35% of the subjects had ADHD
Kupermann et al., 2001 (23)	Prevalence; community-based; 54 adolescents with AUD	Higher rate of ADHD than general population; ADHD preceded CD diagnosis, which preceded AUD
Szobot et al., 2007 (9)	Case-control; community-based; 61 adolescents with SUD and 183 normal controls	ADHD: significant OR (9.12) for SUD, even adjusting for the presence of CD
B) Sample: adults with ADHD		
Biederman et al., 1995 (24)	Longitudinal; compared; clinic; 120 ADHD and 120 controls	ADHD: Higher lifetime risk for psychoactive SUD (52%) than comparison subjects (27%)
Biederman et al., 1998 (25)	Case-control; clinic; 239 ADHD and 268 controls	ADHD: a 2-fold increased risk for SUD
Murphy et al., 2002 (26)	Case-control; 96 ADHD (clinic) and 64 controls (community)	ADHD: higher rates of SUD
C) Sample: adolescents with ADHD		
Weiss et al., 1985 (27)	Longitudinal (15 years); clinic; not blind; 63 ADHD and a control group	No higher rate of SUD among cases in comparison to controls
Biederman et al., 1997 (21)	Longitudinal; clinic; 140 ADHD and 120 controls	Youths with and without ADHD had similar risk for SUD
Molina and Pelham,2003 (17)	Longitudinal; clinic; 142 with ADHD and 100 controls	Persistence of ADHD and CD were each associated with elevated substance use behaviors
Biederman et al., 2006 (28)	Longitudinal (10 years); clinic; 140 ADHD and 120 controls	ADHD: more regular use of nicotine, alcohol and illicit substances (HR= 2.7, 2.3 and 2.2, respectively).
August et al., 2006 (29)	Longitudinal; community-based; 27 ADHD; 82 ADHD+CD or ODD and 91 controls	ADHD: more associated to SUD just in the presence of CD or ODD
D) Sample: adolescents without ADHD or SUD		
Disney et al., 1999 (30)	Prevalence; 626 17-years-old-twins; community-based; both genders	ADHD: no effect over SUD when results were adjusted for the presence of CD
Tapert et al., 2002 (31)	Longitudinal (8 years); community-based; 66 youths without ADHD	Baseline attention/executive scores significantly predicted substance use and dependence symptoms 8 years later
Gau et al., 2007 (32)	Longitudinal (3 years); 428 school children aged 12 years	ADHD independently associated to SUD (HR=3.5)
Fergusson et al., 2007 (33)	Longitudinal (25 years); community-based; birth cohort of 1,265 New-Zealand born children	Early association between early attention problems and further SUD are mediated by conduct problems

Note: ADHD = Attention Deficit/Hyperactivity Disorder; SUD = Substance Use Disorder; AUD = Alcohol Use Disorder; OR = Odds Ratio; HR = Hazard Ratio; CD = Conduct Disorder; ODD = Oppositional Defiant Disorder.

ANEXO 2

Substance Use Disorders in Adolescence

(In press, Advances in Biological Child Psychiatry,
um volume na série 'Advances in Biological Psychiatry')

Substance Use Disorders in Adolescence

Szobot, Claudia M[1] M.D. and Bukstein, Oscar[2] M.D.

[1]Attention Deficit/Hyperactivity Outpatient Program, Hospital de Clínicas de Porto Alegre (HCPA), Federal University of Rio Grande do Sul (UFRGS), Brazil; Center for Drug and Alcohol Research, HCPA, UFRGS, Brazil.

[2]Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, United States. Correspondence: e-mail: BuksteinOG@upmc.edu

Corresponding author for proofs and reprint: Dr. Claudia Szobot. Hospital de Clínicas de Porto Alegre. Programa de Déficit de Atenção/Hiperatividade. Rua Ramiro Barcelos, 2350, sala 2201. CEP 90035-003. Porto Alegre, Brasil. Phone/fax: 55-51-3330-5813

e-mail: cmszobot@terra.com.br

Words in the text: 4,331

ABSTRACT

Substance Use Disorders (SUDs) is one of the most prevalent disorders among adolescents worldwide. Adolescent SUDs can be chronic disorders, resulting in diverse negative outcomes. Adolescents with SUDs generally present one or more psychiatric comorbidities, where the most prevalent are Disruptive Behavior Disorders. SUDs in adolescents have a multivariate etiology, where neurobiology has a relevant role. In this selective review of the literature, we discuss several studies documenting the effects of dopaminergic system dysfunctions, genetics, intra-uterine exposure to drugs, psychiatric comorbidity, age at the first consumption and other issues on further SUDs. An understanding of how neurobiology and/or environmental factors influence SUDs onset and progression can contribute to guide governmental policies toward drugs and preventive SUDs approaches. There is support in the literature for different specific SUDs interventions and some medications have been systematically used in adolescents with SUDs, despite the clear need for more pharmacological trials in this population.

Keywords: Substance Use Disorders, adolescence, etiology, neurobiology

INTRODUCTION

According to the World Health Organization (WHO) (1), psychoactive substances (PS) are substances that, “when taken in or administered into one's system, affect mental processes, e.g. cognition or affect”. It includes both licit and illicit substances, although in most countries the use of any PS by adolescents is not allowed, despite being a “licit” (such as alcohol) or “illicit” (such as cannabis) substance.

First drug contact generally occurs during the adolescence, since this developmental period offers a special context for that (2). Adolescent Substance Use Disorders (SUDs) are a major mental health concern (3, 4) and one of the most prevalent disorders in adolescents (5). Usually, adolescents start experimenting with adult licit (legal) drugs (alcohol and/nicotine) and, afterwards, some will experiment illicit drugs. A subgroup will move on to repeated drug use and SUDs. According to the WHO, the main PS consumed are: nicotine, alcohol and cannabis (6). In the United States (USA), about 3,000 adolescents begin to smoke per day, of which 30% turn into regular users (7). Over 80% of American adolescents have already used alcohol by the end of high school (8). In Australia, 60% of adolescents have already tried cannabis (9). The presence of SUDs has been associated to several negative outcomes: higher criminality rates (10), motorcar accidents (11), school dropout (12), exposure to traumatic situations (13), exposure to sexually transmittable diseases and pregnancy (14) and suicide (15). The frequent use of cannabis resulted in higher chances of developing depression and anxiety in Australian students (9).

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, SUDs reflects a diagnosis of abuse or dependence of drugs (16). For a dependence diagnosis, the adolescent must reach three out of seven symptoms (such as tolerance, withdrawal, or persistent use despite adverse consequences). For an abuse diagnosis, the adolescence must

have a repeated pattern of drug use resulting in one or more (out of four) symptoms (like legal problems). The diagnosis of dependence is sovereign over the abuse diagnosis. Although lately the majority of the studies relies on SUDs diagnoses from DSM-IV TR criteria, some empirical data have suggested the need of a diagnostic system that attend to specific issues relating to adolescents, such as the developmental context of use and a variable distribution of SUD symptoms., since DSM-IV was developed based on adult substance use behavior and sequleae (17). Thus, when evaluating a SUDs diagnosis, especially in a clinical practice setting, clinical judgment is recommended. Finally, some studies present alcohol as a separated category (Alcohol Use Disorders, AUD), in order to distinguish from illicit drug use. Although generally, SUDs have common pathways, research has suggested different pattern of preceding comorbidity and genetic influence according to drug category (for example, alcohol or cannabis), and for experimentation, abuse or dependence. Thus, when studies join drug categories and clinical presentation in etiological studies, some specificity is lost.

THE ROLE OF PSYCHIATRIC COMORBIDITIES

Usually, an adolescent with SUDs have a psychiatric comorbidity. The comorbitidies can just coexist with SUD, have an etiological influence or might be a consequence of drug use. The comorbidities often have a negative impact on SUD, with higher rates of treatment, impaired role functioning, suicide attempts and academic problems (18).

There are several studies suggesting that certain psychopathologies precede the early experimentation (before 13 years of age) or the regular use of drugs. Considering only experimentation of psychoactive substance (PS), a strong association with Oppositional Defiant Disorder (ODD) (OR=4.2; IC95%=1.0-17.8) is found (19). It is known that the presence of mental disorder in childhood is associated to the regular use of marijuana during

adolescence (17.3% vs. 21.5%; RC=1.87; IC95%=1.17-2.98; p < 0,008) (20). The dependence of PS is higher in children/adolescents with Conduct Disorder (CD) (OR=6.0; IC95%=1.7-20.9), ODD (OR=4.1; IC95%=1.1-14.7), Attention Deficit/Hyperactivity Disorder (ADHD) (OR=3.6; IC95%=1.0-13.5), Affective Disorders (OR=3.2; IC95%=1.1-9.3) and Anxiety Disorder (OR=5.5; IC95%=1.8-16.3) (19). Among psychopathologies, CD is the best established as conferring risk to the development of SUDs (21, 22). Recently, it was reported that a diagnosis of CD between 11 and 14 years of age was a powerful predictor of substance disorders by 18 years of age (OR > 4.27), even adjusting for potential confounders (23). Bipolar Disorder was also related to the development of dependence of SPA (19). It is important to note that there might be an interaction between gender, age and comorbidity. For instance, anxiety increased the risk of SUD in girls at age 16, but not before that (24).

It is interesting to note that there are contradictory data in the literature regarding ADHD as an independent risk factor for SUDs, when adjusting results for the presence of Conduct Disorder. CD is highly prevalent among adolescents with ADHD (24, 25, 26) and some evidence suggest that only those ADHD youths with comorbid CD would be at higher risk. Interestingly, studies trying to disentangle the role of ADHD on the development of SUD have contradictory results. It was described that ADHD had no effect over SUDs liability in a longitudinal community-based study in New Zealand (27). In Brazilian adolescents, however, ADHD was associated to a significantly higher OR for illicit SUD, even when results were adjusted for the presence of CD (OR = 9.12; 95% CI = 2.84-29.31, P < 0.01) (28). A recent study in the US replicated these findings, demonstrating that a categorical diagnosis of ADHD was associated to a higher OR for nicotine (OR = 2.1) and illicit PS (OR = 2.82), independently of the presence of CD (23). Thus, although there is no doubt on the effect of CD and ODD on the liability for further SUD, the debate remains open regarding the place of ADHD as a risk factor for SUD in adolescence and later life.

Another interesting point is the association between trauma exposure in childhood/adolescence and further SUDs. It is well documented that children/adolescents who have been exposed to traumatic events have a higher prevalence of SUDs (29-31). Although the occurrence of SUDs in a traumatized child/adolescent may be the result of the interaction between several variables, trauma exposure causes neuroendocrinologic changes that, in turn, might be associated with higher drug propensity. De Bellis (2002) (32) mentions that in a developing brain, elevated levels of catecholamine and cortisol (as a result of traumatic event, such as maltreatment or sexual abuse) may lead to adverse brain development which will result, through different pathways, in maturation failures in frontal and pre-frontal cortex. These stress-induced mechanisms will cause executive impairments, which are clearly implicated in SUD liability, as will be reviewed next.

NEUROBIOLOGY

The dopamine system has long been implicated in alcohol dependence and other substance dependences (33-36). Dopamine-regulated areas such as the basal ganglia and frontal areas are affected in SUD subjects (37). Executive (38) and reward system functions (37) have a strong influence on SUD liability. Thus, children with cognitive dysfunctions (such as ADHD, or CD) might be in high-risk drug use situations, probably as function of poor judgments and tendency in sustaining a behavior despite negative consequences (39). An adolescent with ADHD, for example, might have more difficulties to accurately evaluate the negative consequences of drug use or a high risk situation for drug use, which is an important mechanism in order to avoid drug use. If the adolescent does not properly realize that drug use is resulting in negative consequences, such as family problems, he might have more difficulty in changing to a healthier behavior, due to their impaired cognitive flexibility. Furthermore, individuals with SUD may have dysfunctions in the brain reward system (RS).

The RS is associated with motivation, salience of a stimulus (40) and delay capacity (41). As a result, a youth with RS dysfunction may choose a more immediate but ultimately worst reward rather than delayed gratification for future benefit(s) or make compulsively seek reward from drugs or alcohol at the expense of their immediate or future needs and despite of immediate or future consequences. Impulsive behavior and choices are associated with drug use. Subjects with SUD may decide on choices with high immediate gains in spite of higher future losses (42). Thus, for an adolescent with ADHD, it might be more important getting high, for example, than avoiding legal or academic consequences due to this behavior. This intriguing neurobiological "environmental" might be a result of different components, probably highly interrelated.

Brain imaging studies provide a good method for evaluating brain effects (both on morphology and function) of drug use. The vast majority of brain imaging studies on this field, however, is based on adult samples. Nevertheless, there are some adolescent studies documenting drug effects on brain RS and areas related to executive function, usually with consequences that are not related just to the intoxication period. For instance, blood oxygenation-level dependent (BOLD) functional Magnetic Resonance Imaging (MRI) was performed in 24 chronic marijuana users (12 abstinent and 12 active) and control subjects during a set of visual-attention tasks. Active and abstinent marijuana users showed decreased activation in the right prefrontal, medial and dorsal parietal, and medial cerebellar regions, but greater activation in various frontal, parietal and occipital brain regions during the visual-attention tasks (all with $P \leq 0.001$). Both earlier age of first use and greater estimated cumulative dose of THC exposure were related to lower BOLD signals in the right prefrontal region and medial cerebellum (43). A pilot study with functional MRI found differences in the hippocampus between adolescents with cannabis use vs just tobacco users vs non smokers (44). Another study with MRI and Positron Emission Tomography (PET) evaluated the

effects of age of first cannabis use on brain morphology, finding that subjects who started using marijuana before age 17, compared to those who started later, had smaller whole brain and percent cortical gray matter and larger percent white matter volumes. Functionally, males who started using marijuana before 17 years had significantly higher Cerebral Blood Flow than other males (45). More brain imaging studies are recommended, preferably with longitudinal designs and including both genders (girls are consistently underrepresented).

GENETICS

Genetics carry out an important effect on the risk for SUDs, mainly for more severe cases, as evidenced in different studies (46, 47). Studies with twins showed heritability as a risk factor for the use of nicotine, caffeine, tranquilizers, sedatives and also, marijuana and cocaine dependence (19). In relation to alcohol, Yates et al, (48) demonstrated that genetic factors influence the severeness of the degree of dependence, while lighter degrees would be better explained by environmental factors. Considering cannabis, the heritability estimates range between 0.45 and 0.78 for abuse or dependence, respectively (42). Regarding to alcohol, twin studies indicate that 20-30% of the variation in liability to alcohol initiation might be attributed to genetics, whereas 50-60% of the variation of alcohol progression may be associated to genetics. It is interesting to highlight that besides the direct predisposition to dependence of drugs, genetics can intermediate risk for SUDs by stimulating risk phenotypes for use of SPA. A genoma-wide search for quantitative trait loci, in a community-based sample of 4,493 adolescents and young adults, described molecular genetic basis for the comorbidity between dependence vulnerability and antisocial behavior (same region on chromosome 9q34) (50). In relation to SUDs for cocaine, Guindalini et al. (51) demonstrated that the presence of the allele 3 in a polymorphism at the Dopamine Transporter (DAT1) is associated with a larger risk for abuse of this substance [allele OR=1.2; IC(95%) = 1.01-1.37;

p=0.036; 3/3 homozygote OR=1.45; IC(95%) =1.18-1.78; p=0.0008)] (70). Interestingly, DAT1 was also implicated in ADHD vulnerability, which in turn might have an influence in adolescent SUD (28, 52).

INTRA-UTERINE EXPOSURE

The intra-uterine exposure to drugs has also a role on SUDs liability. Significant alcohol consumption during pregnancy has been associated to attention deficit problems, impulsiveness and cognitive deficits, which are implicated as risk factors for alcohol related disorders. Higher rates of alcohol dependence (15.9%) were observed in subjects without first degree family history of alcoholism but with intra-uterine exposure to alcohol. Through multivariate analysis, controlling for family history, exposure to other substances (nicotine, caffeine, antibiotics, cannabis, among others) and adverse environmental effects such as low socioeconomic level, intra-uterine exposure to alcohol maintained significant association with alcohol related problems at the age of 21 (53). Similarly, it has been shown that intra-uterine nicotine exposure is associated to higher ADHD rates (54), indirectly affecting SUDs liability, since ADHD has been suggested as an independent risk factor to SUDs (28). Smith et al., 2001, (55) examined the possible neurotoxic effects of prenatal cocaine exposure on the developing brain using proton magnetic resonance spectroscopy (1)H-MRS). The authors compared 14 cocaine-exposed children with 12 age-matched unexposed controls. Metabolite concentrations of N-acetyl-containing compounds (NA), total creatine (Cr), choline-containing compounds, myoinositol, and glutamate + glutamine were measured in the frontal white matter and striatum. Children exposed to cocaine in utero had significantly higher Cr (+13%) in the frontal white matter. Recently, the effects of in utero cocaine and polysubstance exposure on the adolescent caudate nucleus was assessed through high-resolution magnetic resonance imaging. The comparison focused on contrasting the control group with high-

exposure subjects (mothers who used cocaine during pregnancy). Results indicated that the caudate (both left and right) was significantly larger in controls versus subjects ($P < 0.0025$), implying cocaine exposure-related detriments to the dopaminergic system. (56). Effects of prenatal cannabis on response inhibition (RI), with functional MRI, showed that with increased prenatal marijuana exposure, there was a significant increase in neural activity in bilateral prefrontal cortex and right premotor cortex during RI, and an attenuation of activity in left cerebellum when challenging the RI neural circuitry. Prenatally exposed offspring had significantly more commission errors than non exposed participants. These findings were observed when controlling for present marijuana use and prenatal exposure to nicotine, alcohol and caffeine, suggesting that prenatal marijuana exposure is related to changes in neural activity during RI that last into young adulthood (57). Regarding to alcohol exposure, a study examined brain metabolism using magnetic resonance spectroscopy (MRS) and searched for regions of specific vulnerability in adolescents and young adults prenatally exposed to alcohol. Ten adolescents and young adults with confirmed heavy prenatal alcohol exposure and a diagnosis within the fetal alcohol spectrum disorders (FASD) were included. Three of them had fetal alcohol syndrome (FAS), 3 had partial FAS (PFAS), and 4 had alcohol-related neurobehavioral disorder (ARND). The control group consisted of 10 adolescents matched for age, sex, head circumference, handedness, and body mass. Three-dimensional (1) H magnetic resonance spectroscopic imaging ((1)H MRSI) was performed in the cerebrum and cerebellum. Metabolite ratios N-acetylaspartate/choline (NAA/Cho), NAA/creatine (Cr) and Cho/Cr, and absolute metabolite intensities were calculated for several anatomic regions. In patients with FASD, lower NAA/Cho and/or NAA/Cr compared with controls were found in parietal and frontal cortices, frontal white matter, corpus callosum, thalamus, and cerebellar dentate nucleus. There was an increase in the absolute intensity of the glial markers Cho and Cr. Results suggestes that prenatal alcohol exposure alters brain

metabolism in a long-standing or permanent manner in multiple brain areas (58). Thus, drug use during pregnancy might result in long-lasting brain morphology and functional changes in the offspring. Interestingly, some studies reported changes on brain structures/functions well recognized in having a role in SUDs liability (frontal and caudate response inhibition); this is of special concern, since these children might also have a higher genetic susceptibility to SUDs.

AGE AT FIRST CONSUMPTION

The age at first consumption has been implicated on SUDs risk. A precocious beginning of use of a PS (around 13 years of age) was related to the fastest evolution toward SUDs (59). A younger age of experimentation was significant predictor for alcohol abuse between 17 and 18 years of age, and subjects that tried alcohol earlier, possessed a larger risk ($p < 0,001$) (60). In spite of these findings, there is a discussion in the literature if the age of first consumption would be an independent risk, or just a marker of, for instance, larger impulsiveness or higher exposure to PS. However, animal studies have strongly suggested an independent effect of early exposure to different drugs and further long-lasting brain changes, usually in the direction of a higher sensitization to drug effects. For instance, nicotine self-administration by adolescent rodents had stronger and longer-lasting effects on nicotine intake in adulthood than initial self-administration by adult rodents (61). Also, the exposure of mice to both methylphenidate (MPH) and 3,4-methylenedioxymethamphetamine (MDMA) during adolescence resulted in long-lasting neural adaptations, including sensitized responses to cocaine-induced reward and psychomotor stimulation following cocaine withdrawal. The animals received intraperitoneal injections of saline, MPH or MDMA, during adolescence period. One month later, when already adults, cocaine-induced conditioned place preference (CPP) and locomotor activity (LMA) were investigated. Previous MPH exposure caused

significantly less CPP. However, two weeks later, after extinction of CPP and withdrawal from cocaine, cocaine was again administered, resulting in a significantly higher CPP in both MPH and MDMA groups, in comparison to the saline group (62)**.** Long-lasting brain effects of early exposure to cannabis have also been documented. It was compared, for example, the effects of repeated cannabinoid administration in adolescent and adult rats on dopamine in mesoaccumbens. In this study, the adolescent group, but not the adult, developed long-lasting cross-tolerance to morphine, cocaine and amphetamine, suggesting a neuronal adaptation of dopaminergic neurons after subchronic cannabinoid intake at a young age, with consequences on subsequent responses to drugs of abuse (63). Different cocaine response, according to different stages of brain maturation, was also documented. Cocaine CPP was evaluated in early adolescent, late adolescent and young adult rats, testing whether age-related differences in cocaine place preferences were related to differences in the mesolimbic dopaminergic system. Measures relied on extracellular dopamine levels in the nucleus accumbens septi of the three 3 groups of rats, via quantitative microdialysis under transient conditions. Results showed that adolescents differed from adults in basal dopamine. There were age-related differences in the extraction fraction (E_d), an indirect measure of dopamine reuptake. Together, these findings suggest ontogenetic differences in extracellular dopamine and dopamine reuptake and that these differences might be implicated in the higher adolescent vulnerability to addiction (64). There is also data documenting long-lasting effects of early alcohol exposure on further dopamine levels, helping to explain the underlying physiological mechanism in adolescent vulnerability to the rewarding properties of ethanol. Recently, it was tested whether chronic ethanol exposure during adolescence would alter nucleus accumbens septi (NAcc) dopamine (DA) levels in the adult brain, in rats. Changes in extracellular DA levels in the anterior NAcc shell were measured via the no net flux (NNF) paradigm. Findings documented greater extracellular DA levels in rats chronically treated with ethanol during

adolescence in comparison with saline-exposed controls (65). Similarly, it was tested the hypothesis that ethanol consumption by alcohol-preferring (P) rats during the periadolescent period would cause persistent alterations in the mesolimbic dopamine (DA) system. The results of the microdialysis experiments suggested that periadolescent ethanol drinking by P rats increased basal DA neurotransmission and prolonged the response of DA neurotransmission to ethanol (66). Another study indicated an age-dependent difference in the homeostatic alterations of mesolimbic systems in response to repeated ethanol treatment, in rats, an effect that may manifest itself as differences in behavioral responsivity and conditionability to the drug and the drug's effects (67). Thus, animal studies strongly support that: a) adolescent brain is more sensitive to drug effects; b) some long–lasting brain effects of drug exposure are age dependent.

GATEWAY THEORY

Despite concerns about the validity of the gateway theory for adolescents who use PS, this theory remains an important paradigm for understanding the development of drug use in adolescents. Certain types of drugs can predispose the pathway for SUDs towards more severe stages. Previous history of tobacco dependence was a factor for the regular use of cannabis (68). In that study, 57.4% of the individuals that reported tobacco dependence confirmed regular use of marijuana, while only 12.5% of the ones that denied such dependence were regular users of marijuana ($p < 0.0001$). Besides, marijuana use was accepted as a trigger (“gateway theory”) for use of other illicit PS. Another study considered the frequency in the use of marijuana as a predictor for SUDs between 16 and 19 years of age (69). However, it is very difficult to conduct a study that really “proves” the gateway hypothesis, in its real meaning, in real world. According to marijuana gateway theory, for example, the use of cannabis would increase the risk for the use of other drugs. Thus, studies

should differentiate the effects of cannabis exposure *per se*, from, for instance, the effect of a common propensity. In addition, if cannabis really increases the risk for other drug use, would this risk conferred by some neurobiological effect (for example, sensitization), or due to environmental factors (increasing contact with drug use subcultures, or with drug sellers, for instance)? Animal models help answering this question, at least partially, since some strong environmental factors are eliminated in this method (no peer pressure and no drug sellers influences, for instance). In this sense, it was recently described that exposure to cannabis (THC) during adolescence caused specific disturbance of the endogenous opioid system later on, in rats. Striatal preproenkephalin mRNA expression was increased in the nucleus accumbens (NAc) shell and the mu opioid receptor (muOR) GTP-coupling was potentiated in mesolimbic and nigrostriatal brainstem regions in THC-pretreated animals. muOR function in the NAc shell was specifically correlated to heroin intake. Authors conclude that their findings support the gateway hypothesis by demonstrating that adolescence cannabis exposure has an enduring impact on hedonic processing resulting in enhanced opiate intake, possibly as a consequence of alterations in limbic opioid neuronal populations (70). Indeed, the gateway theory is another question that remains open, and that exemplifies how simplistic it would be to try to understand adolescent SUDs in a non integrative model.

TREATMENT: GENERAL ASPECTS

It is well established that some treatment is better than no treatment for adolescents with SUDs. Even so, relapse rates are high (71), making the treatment of adolescents with SUDs a challenging task. Effort has been made in order to identify characteristics of better treatment outcomes. It seems that longer treatment duration or time spent in treatment is associated to better results (72). Also, some staff characteristics might interferer in treatment success (73, 74). The therapist should be aware of adolescent cognitive and developmental

characteristics. There is evidence supporting the use of several specific psychosocial interventions for adolescent SUD, such as Cognitive Behavior Therapy, Motivational Therapy (75) and Family Therapy (76). It is important to note that an expressive number of adolescents with SUDs will have one or more coexisting psychiatric comorbidities, which should be properly addressed (3). Some comorbidities will require medication and there is some evidence for the use of lithium for Bipolar comorbidity (77), bupropion for Attention Deficit/ Hyperactivity Disorder (ADHD) comorbidity (78) and for mood disorders comorbidities (79) and fluoxetine for depression comorbidity (80, 81). There is a strong need for more pharmacological trials in adolescents with SUDs with other psychiatric disorders. Taking ADHD as an example, there is report of a 44% prevalence of ADHD among male adolescents with illicit SUD in a community-based study (28). Despite the evidences that ADHD is associated to a worse SUDs prognosis for alcohol and cannabis (82, 83), few treatment studies were conducted in this dually-diagnosed population. Several evidence-based guidelines suggest that stimulants (e.g., methylphenidate - MPH) should be the first option for treatment of ADHD (see, for instance, reference 84), but ADHD treatment studies typically exclude individuals with drug use/misuse or SUD. Since ADHD (85), MPH (86) and most abused drugs (38, 87-89) are associated with dysfunctions and/or actions on dopaminergic system, MPH clinical and neurobiological effects might not necessarily be generalized to this dually-diagnosed population. Cocaine, for example, increases dopamine (DA) by blocking striatal dopamine transporter (DAT) (90), the same target of MPH. Moreover, there is a body of evidence describing that cannabis affects dopamine regulation (89, 91). Thus, MPH clinical effect might not be the same in the context of acute or chronic drug exposure, highlighting the need of treatment protocols derived from studies based on ADHD/SUD samples, and not just on ADHD or ADHD plus other comorbidities. At last, although acamprosate (92) and naltrexone have been evaluated in adults with SUD (93), to the best of our knowledge we

were able to find just one published study with acamprosate in adolescents (94), and no treatment study with naltrexone.

Given the high prevalence, the severity of the associated outcomes and the difficulties in keeping an adolescent engaged into treatment programs for enough time, probably the most important issue in adolescent SUDs is the role of primary prevention. Effective preventive strategies involve different perspectives, such as governmental policies regarding drug use and recognition of early predictors of SUDs. The fact that a significant group of adults with SUD have the onset of their SUD diagnosis before the age 18 years corroborates this idea (95). In this sense, it is well known that adolescent SUDs have a multivariate etiology, with the influence of both biological and environmental variables (96, 97).

CONCLUSIONS

In conclusion, there is significant evidence for the role of neurobiological aspects on SUDs liability. The earlier the exposure of first drug use, the higher the risk for drug problems. This fact probably reflects a combination between a higher neurobiological propensity for SUDs in children and adolescents, in comparison to adults, an the effect of drugs in subjects with less developed brain processes and social skills, due to young age, or several other environmental, family and individual aspects. From a clinical perspective, it is very important to delay the age at first use of nicotine, alcohol and other drugs. Much attention should be given to those children with externalizing disorders, including high impulsivity as well as those with evidence of mood deregulation or internalizing disorders. If the adolescent already has a SUDs diagnosis, specific treatment should be offered, preferable by professionals who are familiar with child and adolescent psychopathology, as well as intervention targeting comorbid psychopathology.

Conflict of interest: Dr. Szobot: Janssen-Cilag speaker's bureau. Travel support by Novartis in the last year. Dr.Bukstein: Shire Pharmcueticals – consultant, research support, and speaker's bureau; McNeil pediatrics – speaker's bureau, consultant; Eli Lilly – research support; Novartis – speaker's bureau.

REFERENCES

1. World Health Organization (WHO) – [cited 2007 Oct 17th]. Available from: http://www.who.int/substance_abuse/terminology/psychoactive_substances/en/index.html.
2. Tarter RE. Etiology of adolescent substance abuse: a developmental perspective. Am J Addict. 2002; 11:171-91.
3. Bukstein OG, Bernet W, Arnold V, Beitchman J, Shaw J, Benson RS, Kinlan J, McClellan J, Stock S, Ptakowski KK. Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. J Am Acad Child Adolesc Psychiatry 2005; 44:609-21.
4. Galduroz JC, Noto AR, Nappo SA, Carlini EA. Household survey on drug abuse in Brazil: study involving the 107 major cities of the country--2001. Addict Behav 2005; 30:545-56.
5. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry. 2003 Aug;60(8):837-44.
6. WHO – [cited 2006 Jan 8]. Available from: http://www.who.int/substance_abuse/facts/cannabis/en/index.html.
7. Van Den Bree MBM, Whitmer MD, Pickworth Wallace B. Predictors of smoking development in a population-based sample of adolescents: a prospective study. Journal of Adolescent Health, 2004 Sept; 35(3):172-81.
8. Johnston LD, O´Malley PM, Bachman JG. Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings, 2000. Bethesda, Md: National Institute on Drug Abuse; 2001.

9. Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey MHW. Cannabis use and mental health in young people: cohort study. BMJ, 2002; 325(7374):1195-8.
10. Feliz-Ortiz M, Velásquez JAV, Medina-Mora ME, Newcomb MD. Adolescent drug use in México and among Mexican-Americann adolescents in United States environmental influences and individual characteristics. Cultur Divers Ethnic Minor Psychol, 2001;7(1):27-46.
11. Mckinnon SA, O´Rourke KM, Thompson SE, Berumen JH. Alcohol use and abuse by adolescents: the impact of living in a border community. J Adolesc Health 2004; 34(1):88-93.
12. De Micheli D, Formigoni ML. Drug use by Brazilian students: associations with family, psychosocial, health, demografic and behavioral characteristics. Addiction, 1999 May;(5):570-8.
13. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WN, Anda RF. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: The adverse childhood experiences study. Pediatrics 2003; 111(3):564-72.
14. Huizinga D, Loeber R, Thornberry TP. Longitudinal study of delinquency, drug use, sexual activity, and pregnancy among children and youth in three cities.Public Health Rep, 1993;108(1):90-6.
15. Fergusson DM, Horwood LJ, Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. Addiction, 2002 Sep; 97(9):1123-35.
16. American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders, (4th edition). Washington, DC, American Psychiatric Association.
17. Winters KC, Latimer W, Stinchfield RD. The DSM-IV criteria for adolescent alcohol and cannabis use disorders. J Stud Alcohol. 1999 May;60(3):337-44.

18. Lewinsohn PM, Rohde P, Seeley JR. Adolescent psychopathology: III. The clinical consequences of comorbidity. J Am Acad Child Adolesc Psychiatry. 1995 Apr;34(4):510-9.
19. Merikangas KR, Avenevoli S. Implications of genetic epidemiology for the prevention of substance use disorders. Addictive Behaviors,2000; 25(6):807-20.
20. Hofler M, Lieb R, Perkonigg A, Schuster P, Sonntag H, Wittchen HU. Covariates of cannabis use progression in a representative sample of adolescents: a prospective examination of vulnerability and risk factors. Addiction, 1999; 94(11):1679-94.
21. August, Gerald J.; Winters, Ken C., PhD; Realmuto, George M., M.D.; Fahnhorst, Tamara, M.P.H; Botzet, Andria, M.A.; Lee, Susanne, PhD. Prospective Sstudy of Adolescent Drug Use Among Community Samples of ADHA and Non-ADHD Participants. J Am Acad Child Adolesc Psychiatry, 2006 July; 45(7):824-31.
22. Biederman J, Wilens T, Mick E, Faraone SV, Weber W, Curtis S, Thornell A, Pfister K, Jetton JG, Soriano J. Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry, 1997; 36:21-9.
23. Elkins I, McGue M, Iacono W. Prospective Effects of Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Sex on Adolescent Substance Use and Abuse. Arch Gen Psychiatry 2007;64 1145-1152.
24. Sung M, Erkanli A, Angold A, Costello EJ. Effects of age at first substance use and psychiatric comorbidity on the development of substance use disorders. Drug and Alcohol Dependence,2004; 75:287-299.
25. Myers MG, Stewart DG, Brown SA. Progression from conduct disorder to antisocial personality disorder following treatment for adolescent substance abuse. Am J Psychiatry. 1998; 155(4):479-85.

26. Clark DB, Cornelius JR, Kirisci L, Tarter RE. Childhood risk categories for adolescent substance involvement: a general liability typology. Drug Alcohol Depend 2005; 77:13-21.
27. Fergusson DM, Horwood LJ, Ridder EM. Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. Drug Alcohol Depend. 2007 Apr;88 Suppl 1:S14-26.
28. Szobot CM, Rohde LA, Bukstein O, Molina BS, Martins C, Ruaro P, Pechansky F. Is attention-deficit/hyperactivity disorder associated with illicit substance use disorders in male adolescents? A community-based case-control study. Addiction. 2007 Jul;102(7):1122-1130.
29. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. Pediatrics. 2003 Mar;111(3):564-72.
30. Ompad DC, Ikeda RM, Shah N, Fuller CM, Bailey S, Morse E, Kerndt P, Maslow C, Wu Y, Vlahov D, Garfein R, Strathdee SA. Childhood sexual abuse and age at initiation of injection drug use. Am J Public Health. 2005 Apr;95(4):703-9.
31. Jaycox LH, Ebener P, Damesek L, Becker K. Trauma exposure and retention in adolescent substance abuse treatment. J Trauma Stress. 2004 Apr;17(2):113-21.
32. De Bellis MD. Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. Psychoneuroendocrinology. 2002 Jan-Feb;27(1-2):155-70
33. Koob, GF and Bloom, FE. Cellular and molecular mechanisms of drug dependence. Science. 1988; 242:715-723.
34. Volkow ND, Wang GJ, Fowler JS, Ding YS. Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for Attention-Deficit/Hyperactivity Dosrder. Biological Psychiatry. 2005; 57(11):1410-1415.

35. Volkow ND, Wang GJ, Begleiter H, Porjesz B, Fowler JS, Telang F, Wong C, Ma Y, Logan JG, Alexoff D, Thanos PK. High levels of Dopamine D2 receptors in unaffected members of alcoholic famililes: Possible protective factors. Archives of General Psychiatry. 2006; 63(9):999-1008.
36. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychological Review 1987; 94:469-492.
37. Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology. 2004;47 Suppl 1:3-13.
38. Tarter RE, Kirisci L, Mezzich A, Cornelius JR, Pajer K, Vanyukov M, Gardner W, Blackson T, Clark D. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. Am J Psychiatry 2003; 160:1078-85.
39. Nigg JT, Casey BJ. An integrative theory of attention-deficit/ hyperactivity disorder based on the cognitive and affective neurosciences. Dev Psychopathol 2005; 17:785-806.
40. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005; 162:1403-13.
41. Sonuga-Barke EJ. Psychological heterogeneity in AD/HD--a dual pathway model of behaviour and cognition. Behav Brain Res 2002; 10:29-36.
42. Bechara A, Martin EM. Impaired decision-making related to working memory deficits in individuals with substance addictions. Neuropsychology 2004; 18:152-62.
43. Chang L, Yakupov R, Cloak C, Ernst T. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain. 2006 May;129(Pt 5):1096-112.
44. Jacobsen LK, Mencl WE, Westerveld M, Pugh KR. Impact of cannabis use on brain function in adolescents. Ann N Y Acad Sci. 2004 Jun;1021:384-90.

45. Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. J Addict Dis. 2000;19(1):1-22.
46. Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Nong L, Meyer JM, Eaves L. Genetic influences on abuse of illicit drugs: A study of 3372 twin pairs. American Journal of Medical Genetics, 1996; 5:473-477.
47. Van Den Bree MB, Johnson EO, Neale MC, Pickens RW. Genetic and environmental influences on drug use and abuse/dependence in male and female twins. Drug Alcohol Depend, 1998 Nov 1; 52(3): 231-41.
48. Yates, WR, Cadoret RJ, Troughton E, Stewart MA. An adoption study of DSM-IIIR alcohol and drug dependence severity. Drug and Alcohol Dependence, 1996; 41:9-15.
49. Agrawal A, Lynskey MT. The genetic epidemiology of cannabis use, abuse and dependence. Addiction. 2006 Jun;101(6):801-12.
50. Stallings MC, Corley RP, Dennehey B, Hewitt JK, Krauter KS, Lessem JM, Mikulich-Gilbertson SK, Rhee SH, Smolen A, Young SE, Crowley TJ. A genome-wide search for quantitative trait Loci that influence antisocial drug dependence in adolescence. Arch Gen Psychiatry. 2005 Sep;62(9):1042-51.
51. Guindalini C, Howard M, Haddley K, Laranjeira R, Collier D, Ammar N, Craig I, O'Gara C, Bubb VJ, Greenwood T, Kelsoe J, Asherson P, Murray RM, Castelo A, Quinn JP, Vallada H, Breen G. A dopamine transporter gene functional variant associated with cocaine abuse in a Brazilian sample. Proc Natl Acad Sci U S A. 2006 Mar 21;103(12):4552-7.
52. Roman T, Szobot C, Martins S, Biederman J, Rohde LA, Hutz MH. Dopamine transporter gene and response to methylphenidate in attention-deficit/hyperactivity disorder. Pharmacogenetics. 2002 Aug;12(6):497-9.

53. Baer JS, Sampson PD, Barr HM, Connor PD, Streissguth AP. A 21 year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking. Arch Gen Psychiatry, 2003; 60:377-85.
54. Schmitz M, Denardin D, Laufer Silva T, Pianca T, Hutz MH, Faraone S, Rohde LA. Smoking during pregnancy and attention-deficit/hyperactivity disorder, predominantly inattentive type: a case-control study. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1338-45.
55. Smith LM, Chang L, Yonekura ML, Gilbride K, Kuo J, Poland RE, Walot I, Ernst T. Brain proton magnetic resonance spectroscopy and imaging in children exposed to cocaine in utero. Pediatrics. 2001 Feb;107(2):227-31.
56. Avants BB, Hurt H, Giannetta JM, Epstein CL, Shera DM, Rao H, Wang J, Gee JC. Effects of heavy in utero cocaine exposure on adolescent caudate morphology. Pediatr Neurol. 2007 Oct;37(4):275-9.
57. Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. Neurotoxicol Teratol. 2004 Jul-Aug;26(4):533-42
58. Fagerlund A, Heikkinen S, Autti-Rämö I, Korkman M, Timonen M, Kuusi T, Riley EP, Lundbom N Brain metabolic alterations in adolescents and young adults with fetal alcohol spectrum disorders. Alcohol Clin Exp Res. 2006 Dec;30(12):2097-104.
59. Sung M, Erkanli A, Angold A, Costello EJ. Effects of age at first substance use and psychiatric comorbidity on the development of substance use disorders. Drug and Alcohol Dependence, 2004; 75:287-299.
60. Hawkins JD, Graham JW, Maguin E, Abbott R, Hill K, Catalano RF. Exploring the Effects of Age of Alcohol Use Iniation and Psychosocial Risk Factors on Subsequent Alcohol Misuse. J of Stud on Alcohol, 1997:280-290.

61. Levin ED, Rezvani AH, Montoya D, Rose JE, Swartzwelder HS. Adolescent-onset nicotine self-administration modeled in female rats. Psychopharmacology (Berl). 2003 Sep;169(2):141-9.
62. Achat-Mendes C, Anderson KL, Itzhak Y. Methylphenidate and MDMA adolescent exposure in mice: long-lasting consequences on cocaine-induced reward and psychomotor stimulation in adulthood. Neuropharmacology. 2003 Jul;45(1):106-15.
63. Pistis M, Perra S, Pillolla G, Melis M, Muntoni AL, Gessa GL. Adolescent exposure to cannabinoids induces long-lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. Biol Psychiatry. 2004 Jul 15;56(2):86-94.
64. Badanich KA, Adler KJ, Kirstein CL. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. Eur J Pharmacol. 2006 Nov 21;550(1-3):95-106.
65. Badanich KA, Maldonado AM, Kirstein CL.Chronic ethanol exposure during adolescence increases basal dopamine in the nucleus accumbens septi during adulthood. Alcohol Clin Exp Res. 2007 May;31(5):895-900.
66. Sahr AE, Thielen RJ, Lumeng L, Li TK, McBride WJ. Long-lasting alterations of the mesolimbic dopamine system after periadolescent ethanol drinking by alcohol-preferring rats. Alcohol Clin Exp Res. 2004 May;28(5):702-11.
67. Philpot R, Kirstein C. Developmental differences in the accumbal dopaminergic response to repeated ethanol exposure. Ann N Y Acad Sci. 2004 Jun;1021:422-6.
68. Hofler M, Lieb R, Perkonigg A, Schuster P, Sonntag H, Wittchen H. Covariates of cannabis use progression in a representative sample of adolescents: a prospective examination of vulnerability and risk factors. Addiction, 1999; 94(11):1679-94.
69. Kirisci L, Tarter R, Vanyukov M, Reynolds M, Habeych M. Relation between cognitive distortions and neurobehavior disinhibition on the development of substance use during

adolescence and substance use disorder by young adulthood: a prospective study. Drug and Alcohol Dependence, 2004; 76:125-133.

70. Ellgren M, Spano SM, Hurd YL. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. Neuropsychopharmacology. 2007 Mar;32(3):607-15.
71. Doyle H, Delaney W, Tobin J. Follow-up study of young attenders at an alcohol unit. Addiction. 1994 Feb;89(2):183-9.
72. Kaminer Y. Adolescent Substance Abuse: A Comprehensive Guide to Theory and Practice. New York, Plenum, 1994.
73. Friedman AS, Schwartz R, Utada A. Outcome of a unique youth drug abuse program: a follow-up study of clients of Straight, Inc. J Subst Abuse Treat. 1989;6(4):259-68.
74. Catalano RF, Hawkins JD, Wells EA, Miller J, Brewer D. Evaluation of the effectiveness of adolescent drug abuse treatment, assessment of risks for relapse, and promising approaches for relapse prevention. Int J Addict. 1990-1991 Aug;25(9A-10A):1085-140.
75. Sampl S, Kadden R. Motivational Enhancement Therapy and Cognitive Behavioral Therapy for Adolescent Cannabis Users: 5 sessions. 2002. Cannabis Youth Treatment Series, volume 1. Substance Abuse and Mental Health Services Administration; Cannabis Youth Treatment (CYT) Manual Series, 4. Rockville, MD: Center for Substance Abuse.
76. Santisteban DA, Szapocznik J. Bridging theory research and practice to more successfully engage substance abusing youth and their families into therapy. J Child Adolesc Substance Abuse 1994; 3:9-24.
77. Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, Heath J. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry. 1998 Feb;37(2):171-8.

78. Riggs PD, Leon SL, Mikulich SK, Pottle LC. An open trial of bupropion for ADHD in adolescents with substance use disorders and conduct disorder. J Am Acad Child Adolesc Psychiatry. 1998; 37(12):1271-8.
79. Solhkhah R, Wilens TE, Daly J, Prince JB, Van Patten SL, Biederman J. Bupropion SR for the treatment of substance-abusing outpatient adolescents with attention-deficit/hyperactivity disorder and mood disorders. J Child Adolesc Psychopharmacol. 2005; 15(5):777-86.
80. Cornelius JR, Clark DB, Bukstein OG, Kelly TM, Salloum IM, Wood DS. Fluoxetine in adolescents with comorbid major depression and an alcohol use disorder: a 3-year follow-up study. Addict Behav. 2005 May;30(4):807-14.
81. Cornelius JR, Bukstein OG, Birmaher B, Salloum IM, Lynch K, Pollock NK, Gershon S, Clark D. Fluoxetine in adolescents with major depression and an alcohol use disorder: an open-label trial. Addict Behav. 2001 Sep-Oct;26(5):735-9.
82. Ercan ES, Coskunol H, Varan A, Toksoz K. Childhood attention deficit/hyperactivity disorder and alcohol dependence: a 1-year follow-up. Alcohol Alcohol 2003; 38(4):352-6.
83. White AM, Jordan JD, Schroeder KM, Acheson SK, Georgi BD, Sauls G, Ellington RR, Swartzwelder HS. Predictors of relapse during treatment and treatment completion among marijuana-dependent adolescents in an intensive outpatient substance abuse program. Subst Abus. 2004; 25(1):53-9.
84. Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M; Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45(6):642-57.

85. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. Ambul Pediatr. 2007 Jan-Feb;7(1 Suppl):73-81.

86. Spencer TJ, Biederman J, Ciccone PE, Madras BK, Dougherty DD, Bonab AA, Livni E, Parasrampuria DA, Fischman AJ. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatry. 2006 Mar;163(3):387-95.

87. Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. Alcohol Alcohol. 2005 Jan-Feb;40(1):2-14.

88. Koob GF. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. Addiction. 2006 Sep;101 Suppl 1:23-30.

89. Tzavara ET, Li DL, Moutsimilli L, Bisogno T, Di Marzo V, Phebus LA, Nomikos GG, Giros B. Endocannabinoids activate transient receptor potential vanilloid 1 receptors to reduce hyperdopaminergia-related hyperactivity: therapeutic implications. Biol Psychiatry. 2006 Mar 15;59(6):508-15.

90. Volkow ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley JS, Dewey S, Ashby C, Liebermann J, Hitzemann R, et al. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry. 1995 Jun;52(6):456-63.

91. Price DA, Owens WA, Gould GG, Frazer A, Roberts JL, Daws LC, Giuffrida A. CB(1)-independent inhibition of dopamine transporter activity by cannabinoids in mouse dorsal striatum.

92. Baltieri DA, de Andrade AG.Efficacy of acamprosate in the treatment of alcohol-dependent outpatients. Rev Bras Psiquiatr. 2003 Sep;25(3):156-9.

93. Morley KC, Teesson M, Reid SC, Sannibale C, Thomson C, Phung N, Weltman M, Bell JR, Richardson K, Haber PS. Naltrexone versus acamprosate in the treatment of alcohol dependence: A multi-centre, randomized, double-blind, placebo-controlled trial. Addiction. 2006 Oct;101(10):1451-62.
94. Niederhofer H, Staffen W. Acamprosate and its efficacy in treating alcohol dependent adolescents. Eur Child Adolesc Psychiatry. 2003 Jun;12(3):144-8.
95. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry 2003; 60:709-17.
96. Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. Am J Psychiatry 2003 Apr;160(4):687-95.
97. Callas PW, Flynn BS, Worden JK. Potentially modifiable psychosocial factors associated with alcohol use during early adolescence. Addict Behav. 2004 Nov;29(8):1503-15.

ANEXO 3

RESOLUÇÕES

HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
GRUPO DE PESQUISA E PÓS-GRADUAÇÃO / COMITÊ DE ÉTICA

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

RESOLUÇÃO

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 03-319 **Versão do Projeto:** 23/06/2004 **Versão do TCLE:** 13/07/2004

Pesquisadores:
FLAVIO PECHANSKY
CLAUDIA MACIEL SZOBOT
LUIS AUGUSTO PAIM ROHDE

Título: TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O SEU TRATAMENTO FARMACOLÓGICO COM A ATOMOXETINA

Este projeto foi Aprovado em seus aspectos éticos e metodológicos, inclusive quanto ao seu Termo de Consentimento Livre e Esclarecido, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde. Os membros do CEP/HCPA não participaram do processo de avaliação dos projetos onde constam como pesquisadores. Toda e qualquer alteração do Projeto, assim como os eventos adversos graves, deverão ser comunicados imediatamente ao CEP/HCPA. Somente poderão ser utilizados os Termos de Consentimento onde conste a aprovação do GPPG/HCPA.

Porto Alegre, 16 de julho de 2004.

Profª Themis Reverbel da Silveira
Coordenadora do GPPG e CEP-HCPA

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

RESOLUÇÃO

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 03-319

Pesquisador Responsável:
FLAVIO PECHANSKY

Título: TRANSTORNO DE DÉFICIT/ATENÇÃO HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO

EMENDA 1

Data da Versão: 19/07/2004

Este documento referente ao projeto acima foi Aprovado em seus aspectos éticos e metodológicos, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde.

Porto Alegre, 27 de julho de 2004.

Profª Themis Reverbel da Silveira
Coordenadora do GPPG e CEP-HCPA

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

RESOLUÇÃO

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 03-319

Pesquisador Responsável:
FLAVIO PECHANSKY

TÍTULO ALTERADO

Título: TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O SEU TRATAMENTO FARMACOLÓGICO COM A ATOMOXETINA

Data da Versão:
19/07/2004

EMENDA 1

Este documento referente ao projeto acima foi Aprovado em seus aspectos éticos e metodológicos, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde.

Porto Alegre, 27 de julho de 2004.

Profª Themis Reverbel da Silveira
Coordenadora do GPPG e CEP-HCPA

Porto Alegre, 19 de julho de 2004

Ao Grupo de Pesquisa e Pós-Graduação
Comissão de Ética em Pesquisa
Nesse Hospital

Emenda ao Projeto: GPPG-03319: Transtorno de Déficit/Atenção Hiperatividade e Abuso de Substâncias em Adolescentes: Estudo sobre a sua associação e sobre o seu tratamento farmacológico com atomoxetina

Prezados colegas:

Solicitamos a avaliação da adequação da seguinte alteração no referido projeto:

1) Modificação do título para: "Transtorno de Déficit/Atenção Hiperatividade e Abuso de Substâncias em Adolescentes: Estudo sobre a sua associação", na medida em que a atomoxetina (medicação que seria testado na segunda fase do estudo) não está ainda disponível ou aprovada pela ANVISA no Brasil. Assim, conforme entendimentos com a empresa Eli-Lilly (patrocinadora do projeto) realizaremos apenas a fase I do estudo (a parte epidemiológica). Fica desde já garantido o fornecimento de tratamento assistencial convencional aos pacientes identificados, bem como o registro dos dados desse atendimento da forma convencional no PRODAH-HCPA. Conforme acerto com a empresa Eli-Lilly, o suporte financeiro ao projeto seguirá no mesmo valor, apenas concentrado na fase epidemiológica. Se a aprovação da medicação pela ANVISA ocorrer durante a execução desse projeto, será ativada a segunda parte do projeto (estudo aberto com a medicação) conforme consta no projeto aprovado e com o uso da verba recebida, mediante discussão com a Eli-Lilly para fornecimento da medicação e consulta a comissão de ética via emenda. Não há necessidade de modificação no Termo de Consentimento Livre e Esclarecido, pois haviam sido elaborados TCLE diferentes para cada etapa de pesquisa.

Atenciosamente,

Flavio Pechansky
Professor Adjunto de Psiquiatria – UFRGS
Coordenador do projeto

Luis Augusto Rohde
Professor Adjunto de Psiquiatria – UFRGS
Co-coordenador do projeto

19 JUL 2004

Anexo I: **TERMO DE CONSENTIMENTO PÓS-INFORMAÇÃO 1**

TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O SEU TRATAMENTO FARMACOLÓGICO COM A ATOMOXETINA

Você está sendo convidado a participar de uma triagem para um estudo desenvolvido pela Universidade Federal do Rio Grande do Sul, Departamento de Psiquiatria, Programa de Transtorno de Déficit de Atenção/Hiperatividade (TDAH) e Centro de Pesquisas e Álcool e Drogas. Trata-se de um estudo a respeito da prevalência do TDAH em usuários de substâncias psicoativas. Nesta etapa, estamos entrevistando adolescentes masculinos, com idade entre 15 e 19 anos. O TDAH é uma condição psiquiátrica que afeta a concentração, a atividade motora e o controle dos impulsos, acarretando em, por exemplo, distrações, esquecimentos, desorganização, mexer-se demais e falar demais.

1. Quais são os meus direitos?

A sua participação é voluntária. A nossa equipe assume um compromisso com você de absoluto sigilo das informações. Você tem o direito de não participar desta pesquisa.

2. Em que consiste a triagem?

Você será solicitado a responder a um questionário com algumas perguntas sobre seus hábitos alimentares, bem como a um questionário da Organização Mundial de Saúde, com 8 perguntas, bem sobre uso de drogas. Reforçamos que possivelmente você será

convidado para a etapa seguinte deste estudo independentemente do resultado no questionário, pois estaremos investigando tanto usuários quanto não usuários de drogas.

3. E após a triagem, o que acontece?

Você estará sendo aguardado no Ambulatório do Hospital de Clínicas de Porto Alegre (HCPA) para uma entrevista mais prolongada, para uma avaliação psiquiátrica. Neste dia, é importante que um de seus pais compareça com você. Reforçamos que a equipe não conversará com os seus pais na sua ausência. Caso você e seus pais não possam comparecer no dia e na data marcadas, um membro de nossa equipe lhe procurará no endereço fornecido.

4. O que eu ganho participando deste estudo?

Você estará contribuindo com um estudo inédito em nosso meio, que poderá ajudar várias crianças e adolescentes em risco para uso de drogas.

Você também receberá uma avaliação psiquiátrica, realizada por uma equipe com ampla experiência na saúde mental de crianças e de adolescentes. Caso você apresente algum problema como TDAH, por exemplo, você poderá iniciar o seu tratamento no Programa de Déficit de Atenção/Hiperatividade do HCPA. Se além do TDAH você também apresentar uso de drogas, você será convidado a participar de outro estudo desenvolvido pela nossa equipe, incluindo tratamento. Caso você apresente outro transtorno psiquiátrico, você será notificado e faremos, com a sua concordância, o seu encaminhamento para outro profissional da rede pública, já com a sua avaliação psiquiátrica realizada.

Você pode entrar em contato com o Dr. Flávio Pechansky ou com a Dra. Claudia M. Szobot através do telefone 51-33305813.

Declaro estar de acordo com os termos aqui expostos, aceitar participar da triagem e, se necessário, realizar a avaliação explicada no item 3.

Nome completo:

Data de Nascimento:

Endereço:

Telefone:

Assinatura:

Nome completo do responsável:

Assinatura do responsável:

Assinatura do pesquisador:

Anexo 2: **TERMO DE CONSENTIMENTO PÓS-INFORMAÇÃO 2**

TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O SEU TRATAMENTO FARMACOLÓGICO COM A ATOMOXETINA: Fase A.

Você está sendo convidado a participar de um estudo desenvolvido pela Universidade Federal do Rio Grande do Sul, Departamento de Psiquiatria, Programa de Transtorno de Déficit de Atenção/Hiperatividade (TDAH) e Centro de Pesquisas e Álcool e Drogas. Trata-se de um estudo a respeito da prevalência do TDAH em usuários de drogas. O TDAH é uma condição psiquiátrica que afeta a concentração, a atividade motora e o controle dos impulsos, acarretando em, por exemplo, distrações, esquecimentos, desorganização, mexer-se excessivamente e falar demais. Nesta fase, estamos entrevistando tanto usuários quanto não usuários de drogas para responderem algumas perguntas e não será proposto nenhum uso de remédio.

1. **Quais são os meus direitos?**

A sua participação é voluntária. Você tem o direito de não participar desta pesquisa.

2. **Qual a minha participação?**

Você responderá a algumas perguntas sobre sintomas psiquiátricos, aplicadas por membro de nossa equipe. Você também fará um teste cognitivo, aplicado por uma psicóloga. Neste teste, você responderá a algumas perguntas, de forma a obtermos o seu Quociente de Inteligência (QI). Um de seus pais será questionado, na sua presença, sobre sintomas de

TDAH e Transtorno de Conduta (transtorno que começa na infância ou na adolescência, associado a condições como brigas, mentiras e matar aulas). A entrevista com seus pais dever durar ao redor de 30 minutos e com você ao redor de uma hora. Depois, você nos fornecerá uma amostra de urina onde, na sua presença, será testada a presença se substâncias sugestivas de uso de drogas.

3. O que será feito com as minhas informações?

As suas informações e possíveis diagnósticos derivados, como Depressão (ficar muito triste, irritado ou desinteressado, por vários dias consecutivos) são absolutamente sigilosos e serão repassados a você mesmo.

Os seus resultados serão incluídos em um banco de dados (onde você será identificado por uma sigla) do nosso grupo, cujos resultados, em conjunto com os resultados de outros adolescentes, serão analisados. Ou seja, teremos resultados de um grupo de pacientes, sem identificação nominal ou que permita o reconhecimento pessoal dos integrantes, e é isto que eventualmente apresentaremos em ocasiões e publicações científicas, garantido o anonimato de sujeitos como você que aceitaram auxiliar neste estudo.

4. O que eu ganho participando deste estudo?

Você estará contribuindo com um estudo inédito em nosso meio, que poderá ajudar várias crianças e adolescentes em risco para uso de drogas.

Você também receberá uma avaliação psiquiátrica realizada por uma equipe com ampla experiência na saúde mental de crianças e de adolescentes. Caso você apresente algum problema como TDAH, por exemplo, você poderá iniciar o seu tratamento no Programa de Déficit de Atenção/Hiperatividade do HCPA. Se além do TDAH você também apresentar uso de drogas, você será convidado a participar de outro estudo desenvolvido pela

nossa equipe, que inclui tratamento para os seus problemas. Caso você apresente outro transtorno psiquiátrico, você será notificado e faremos, com a sua concordância, o seu encaminhamento para outro profissional da rede pública, já com a sua avaliação psiquiátrica realizada.

Você pode entrar em contato com o Dr. Flávio Pechansky ou com a Dra. Claudia M. Szobot através do telefone 51-33305813.

Declaro estar de acordo com os termos aqui expostos, aceitar participar deste estudo.

Sujeito número:

Nome completo:

Data de Nascimento:

Endereço:

Telefone:

Assinatura:

Nome completo do responsável:

Assinatura do responsável:

Assinatura do pesquisador:

Anexo 3: **TERMO DE CONSENTIMENTO PÓS-INFORMAÇÃO 3**

TRANSTORNO DE DÉFICIT DE ATENÇÃO/HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O SEU TRATAMENTO FARMACOLÓGICO COM A ATOMOXETINA: Fase B

Você está sendo convidado a participar de um estudo desenvolvido pela Universidade Federal do Rio Grande do Sul, Departamento de Psiquiatria, Programa de Transtorno de Déficit de Atenção/Hiperatividade (TDAH) e Centro de Pesquisas e Álcool e Drogas. Trata-se de um estudo a sobre o tratamento farmacológico do TDAH em adolescentes usuários de drogas. O TDAH é uma condição psiquiátrica que afeta a concentração, a atividade motora e o controle dos impulsos, acarretando em, por exemplo, distrações, esquecimentos, desorganização, mexer-se excessivamente e falar demais. Através deste estudo, analisaremos a resposta dos sujeitos ao remédio atomoxetina, em comparação ao placebo (comprimido que não tem nenhum remédio, ou seja, que não exerce nenhum efeito biológico no seu corpo). Para participar desta fase do estudo, está implícito que você apresenta TDAH e também Abuso de drogas.

1. Quais são os meus direitos?

A sua participação é voluntária e você pode encerrar a sua participação no estudo no momento em que desejar. A nossa equipe assume um compromisso com você de absoluto sigilo das informações. Você tem o direito de não participar desta pesquisa.

2. Qual a minha participação?

Você responderá a algumas perguntas sobre sintomas psiquiátricos, aplicadas por membro de nossa equipe. Você também fará um teste cognitivo, aplicado por uma psicóloga, para avaliar o seu Quociente de Inteligência . Um de seus pais será questionado, na sua presença, sobre sintomas de TDAH e Transtorno de Conduta (transtorno que começa na infância ou na adolescência, associado a condições como brigas, mentiras e matar aulas). A entrevista com seus pais dever durar ao redor de 30 minutos e com você ao redor de uma hora. Se você já participou da Fase A deste mesmo projeto, você já terá feito esta avaliação, sem necessidade de repeti-la.

Inicialmente, você será sorteado para o grupo que receberá a atomoxetina ou para um grupo que receberá o placebo. A duração do estudo é de oito semanas. Você não saberá, ao longo destas semanas, se estará recebendo a atomoxetina ou o placebo e deverá ingerir, pela manhã, a dose de medicamento por nós fornecida.

Você terá cinco consultas, ao longo de oito semanas, onde será revisado com você: gravidade dos sintomas de TDAH, gravidade do seu uso de drogas e efeitos colaterais a medicação fornecida.

Você também participará de quatro sessões de grupo, onde aprenderá mais sobre como lidar com os sintomas do TDAH, sobre as drogas que você usa e sobre como prevenir recaídas de drogas.

3. O que é a Atomoxetina?

A atomoxetina é um remédio já bastante conhecido no meio científico. Já está comprovado que a atomoxetina é capaz de diminuir os sintomas desatenção (esquecimentos, distratibilidade, pouca concentração, etc.), a hiperatividade (mexer-se muito, pular de uma atividade para outra, falar demais) e a impulsividade (respostas precipitadas, interromper os outros) presentes no TDAH. É uma medicação segura, sem efeitos colaterais graves e que pode ser tomada só uma vez ao dia. Você receberá uma dose de acordo com o seu peso e com a sua tolerância.

4. O que é o Placebo?

O Placebo é um comprimido de apresentação igual à atomoxetina, mas sem nenhum remédio dentro. O placebo não tem nenhum efeito biológico no seu corpo.

5. O que será feito com as minhas informações?

As suas informações são absolutamente sigilosos e serão repassadas a você mesmo.

Os seus resultados serão incluídos em um banco de dados (onde você será identificado por uma sigla) do nosso grupo, cujos resultados, em conjunto com os resultados de outros adolescentes, serão analisados. Ou seja, teremos resultados de um grupo de pacientes, sem identificação nominal ou que permita o reconhecimento pessoal dos integrantes, e é isto que eventualmente apresentaremos em ocasiões e publicações científicas, garantido o anonimato de sujeitos como você que aceitaram auxiliar neste estudo.

6. O que eu ganho participando deste estudo?

Você estará contribuindo com um estudo inédito em nosso meio, que poderá ajudar várias crianças e adolescentes em risco para uso de drogas.

Você também receberá uma avaliação psiquiátrica realizada por uma equipe com ampla experiência na saúde mental de crianças e de adolescentes.

No caso de você ser sorteado para receber a atomoxetina, você estará iniciando o tratamento para um problema que você apresenta e que lhe traz prejuízos em sua vida, como nos estudos. Caso você tenha sido designado ao grupo placebo, você estará protelando em 8 semanas o início do seu tratamento para o TDAH, mas você não ficará sem ajuda, pois receberá o tratamento em grupo para os dois problemas: TDAH e uso de drogas.

7. O que será feito quando acabar as oito semanas do estudo?

Se você quiser, poderá ficar em atendimento com a nossa equipe por mais 2 meses. Após este período, você será encaminhado para a outros serviços de Saúde Mental da rede pública.

Você poderá entrar em contato, se necessário, entre as consultas, com o Dr. Flávio Pechansky ou com a Dra. Claudia M. Szobot através do telefone 51-3330-5813.

Declaro estar de acordo com os termos aqui expostos, aceitar participar deste estudo.

Sujeito número:

Nome completo:

Data de Nascimento:

Endereço:

Telefone:

Assinatura:

Nome completo do responsável:

Assinatura do responsável:

Assinatura do pesquisador:

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

RESOLUÇÃO

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 03-319

Pesquisador Responsável:
FLAVIO PECHANSKY

Título: TRANSTORNO DE DÉFICIT/ATENÇÃO HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O EFEITO CEREBRAL ATRAVÉS DE SPECT, E CLÍNICO, DO TRATAMENTO FARMACOLÓGICO COM METILFENIDATO

Data da Versão:

ADENDO 1 : TROCA MEDICAMENTO 14/01/2005

Este documento referente ao projeto acima foi Aprovado em seus aspectos éticos e metodológicos, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde.

Porto Alegre, 22 de março de 2005.

Profª Nadine Clausell
Coordenadora do GPPG e CEP-HCPA

ADENDO 1

NOVA INTERVENÇÃO: METILFENIDATO

Em termos gerais, os objetivos (item 3, pgs 22 e 23) e as hipóteses (item 4, pg 24) seguem os mesmos do projeto original, já aprovado no GPPG, apenas com a substituição da atomoxetina por metilfenidato.

Sobre o metilfenidato (MFD):

O MFD é rapidamente absorvido após a administração oral e atinge o pico plasmático em aproximadamente 2 horas. A meia-vida plasmática é de 1-3 horas e as concentrações no SNC excedem às plasmáticas. O metabolismo é hepático e a excreção é urinária. Em função do breve tempo de ação, a medicação deve ser ingerida de 2 a 3 vezes ao dia, em geral pela manhã e almoço (eventualmente uma menor dose ao redor das 17hs) (Hoffmann e Lefkowitz, 1995). Os principais efeitos colaterais são insônia, dor abdominal, cefaléia, tiques, nervosismo e anorexia. A dose terapêutica situa-se entre 0.3-1.0mg/quilograma/dia, equivalendo normalmente a doses entre 20 a 60 mg/dia (AACAP, 2001).

O MFD no TDAH:

A literatura claramente apresenta os estimulantes como as medicações de primeira escolha para o TDAH (Greenhill, 1999), existindo mais de 150 estudos controlados (destes

mais de 100 com amostras de crianças e adolescentes) demonstrando a sua efetividade à curto prazo no transtorno. Cerca de 70% dos pacientes têm respostas robustas aos psicoestimulantes e os toleram bem (American Academy of Pediatrics, 2001; Spencer et al., 1996). Recentemente, o National Institute of Mental Health (NIMH) Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) estendeu a eficácia, já demonstrada à curto prazo, para 14 meses (The MTA Cooperative Group, 1999). Em alguns países, como nos Estados Unidos (EUA), o psicoestimulante mais prescrito é o MFD (Zarin et al., 1998). No Brasil o único psicoestimulante disponível é o MFD.

O MFD nos pacientes adolescentes com a comorbidade TDAH/uso de drogas:

Há poucos estudos que avaliam o tratamento medicamentoso desta comorbidade, sendo, em sua maioria, com adultos. Schubiner (2002) avaliou através de um ECR o efeito do MFD em 48 adultos usuários de cocaína. Neste estudo, o MFD mostrou-se clinicamente seguro e com efeitos terapêuticos nos sintomas de TDAH. Apesar disto, não houve efeito sobre o uso de cocaína e nem sobre a fissura. Somoza (2004), através de um estudo aberto, com 10 semanas e 41 adultos usuários de cocaína, observou melhora nos sintomas de TDAH e de dependência de cocaína.

Alterações no protocolo com a substituição da atomoxetina pelo MFD:

A seqüência proposta para este protocolo medicamentoso é basicamente a mesma proposta para a atomoxetina, apenas com a substituição da medicação e com o encurtamento do protocolo para quatro semanas (item 5.5 no projeto original, pgs 35 e 36). A redução do

tempo de estudo deve-se ao fato de se atingir dose terapêutica em menor intervalo de tempo com o MFD, e também por ter início de açãō clínica mais rápido.

Os pacientes receberão a medicação na seguinte dosagem:

- Primeira semana: 0,5 mg/quilograma/dia
- Segunda semana: 0,7mg/quilograma/dia
- Terceira e quarta semanas: 1,2 mg/quilograma/dia.

A dose do MFD será dividida em três tomadas diárias (manhã, meio-dia e entardecer). A medicação deve ser administrada pelo adulto responsável.

Os pacientes serão avaliados semanalmente. Em cada consulta, será mensurada a gravidade dos sintomas de TDAH, gravidade do uso de drogas, eventos adversos e aderência ao tratamento por contagem de pílulas. O uso de drogas por teste de urina será avaliado na primeira e na última semana. Os instrumentos estão descritos no projeto original (item 5.4, pgs 28-30), bem como o manejo dos possíveis efeitos adversos (pg 35).

Alterações no orçamento em função da troca de medicação:

O orçamento altera-se no seguinte sentido:

a) Aquisição do MFD: preço médio da caixa com 20 comprimidos = 15,00; dose média por paciente = 0,88mg/quilograma/dia, considerando peso médio de 60 quilos (= aproximadamente 55mg/dia = 5,5 comprimidos). Ao longo de 28 dias (duração do protocolo = aproximadamente 8 caixas por paciente. Considerando-se 25 sujeitos = 200 caixas = 3.000,00

b) Manipulação do Placebo: idêntica quantia ao metilfenidato, ou seja, 3850 comprimidos (5,5 cp X 28 dias, X 25 sujeitos) Valor = 500,00

Total = 3.500,00

REFERÊNCIAS BIBLIOGRÁFICAS:

1. Hoffman, B. B.; Lefkowitz, R. J. Cathecolamines, sympathomimetic drugs, and adrenergic receptor antagonists. *In: Goodman & Gilman's,* The pharmacological basis of therapeutics, pp 199-248, 9ª ed., 1995.

2. AACAP Official Action. Summary of the Practice Parameters for the Use of Stimulant in the Treatment of Children, Adolescents, and Adults. *J Am Acad Adolesc Psychiatry*, 40: 1352-1355, 2001.

3. Greenhill, L. L.; Halperin, J. M.; Abikoff, H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry*, 38(5):503-512, 1999.

4. The MTA Cooperative Group. A 14- month randomized clinical trial of treatment strategies for attention-deficit/hyperativity disorder. *Arch Gen Psychiatry*, 56: 1073-1086, 1999.

5. Zarin, D. A.; Suarez, A. P.; Pincus, H. A.; Kupersanin, E.; Zito, J. M. Clinical and treatment characteristics of children with attention-deficit/hyperactivity disorder in psychiatric practice. *J Am Acad Child Adolesc Psychiatry,* 37:1262-1270, 1998.

6. Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, Lockhart N, Edwards A, Donlin J, Pihlgren E. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. *Exp Clin Psychopharmacol.* 10 (3):286-94, 2002.

7. Somoza EC, Winhusen TM, Bridge TP, Rotrosen JP, Vanderburg DG, Harrer JM, Mezinskis JP, Montgomery MA, Ciraulo DA, Wulsin LR, Barrett JA. An open-label pilot study of methylphenidate in the treatment of cocaine dependent patients with adult attention deficit/hyperactivity disorder. *J Addict Dis.* 23(1):77-92, 2004.

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

RESOLUÇÃO

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 03-319

Pesquisador Responsável:
FLAVIO PECHANSKY

Título: TRANSTORNO DE DÉFICIT/ATENÇÃO HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O EFEITO CEREBRAL ATRAVÉS DE SPECT, E CLÍNICO, DO TRATAMENTO FARMACOLÓGICO COM METILFENIDATO

Data da Versão:

ADENDO 2: EXAMES DE NEUROIMAGEM 14/01/2005

Este documento referente ao projeto acima foi Aprovado em seus aspectos éticos e metodológicos, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde.

Porto Alegre, 22 de março de 2005.

Profª Nadine Clausell
Coordenadora do GPPG e CEP-HCPA

ADENDO 2

INCLUSÃO DE EXAMES DE NEUROIMAGEM

O grupo do PRODAH introduziu, ao longo de 1999, uma linha de pesquisas em neuroimagem e TDAH. Inicialmente, avaliou-se o efeito agudo do metilfenidato em crianças com TDAH, encontrando-se uma redução da perfusão cerebral em nível parietal esquerdo nos sujeitos que receberam esta medicação (Szobot et al., 2003). Posteriormente, correlacionamos os dados de neuroimagem com os de farmacogenética do TDAH, com resultados semelhantes aos de outros grupos internacionais (Szobot et al., 2004; Rohde et al., 2003; Roman et al,, 2003). Agora, podemos dar seguimento a esta linha de pesquisas com a utilização de técnicas mais requintadas de neuroimagem molecular, como será explicado a seguir. A idéia proposta é de incluirmos os exames de neuroimagem molecular antes do início do protocolo medicamentoso com o MFD, e depois ao final do mesmo.

Neuroimagem Molecular no TDAH:

Os estudos com neuroimagem funcional encontram, em sua maioria, alterações em nível fronto-estriatal condizentes com o envolvimento do sistema dopaminérgico (Lou et al., 1989; Zametkin et al., 1993). Os estudos de neuroimagem estrutural referem alterações em detreminadas áreas cerebrais, pré-frontal–estriatal direita (Castellanos et al., 1996), caudato (Filipek et al., 1997; Semrud-Clickman et al., 2000) e cerebelo (Berquin et al., 1998).

Nos últimos anos, desenvolveram-se novas técnicas para a análise de receptores cerebrais. Radiofármacos específicos para a o sistema dopaminérgico, como para o transportador de dopamina (DAT) ([^{99m} Tc]TRODAT-1) e o radiofármaco para a enzima dopa decarboxilase ([^{18}F] DOPA) foram desenvolvidos e tiveram grande utilidade para o estudo das alterações dopaminérgicas no TDAH. Através do [^{99m}Tc]TRODAT-1 foi evidenciado uma maior densidade de DAT no corpo estriado em adultos hiperativos do que em controles (Dresel et al., 2000; Krause et al., 2000). Sugere-se que este aumento de DAT cause uma maior e mais rápida captação da dopamina liberada na fenda sináptica, determinado uma diminuição da ação da dopamina.

Neuroimagem Molecular, Transtornos por Uso de Substâncias Psicoativas e TDAH:

O uso crônico de drogas está associado a um aumento da dopamina extracelular. (Volkow et al., 2004a; Volkow et al., 2004b). Tanto o uso de substâncias psicoativas (SPA) quanto o TDAH envolvem circuitos cerebrais em comum, como *reward/saliency, motivation/drive, inhibitory control/disinhibition, memory and conditioning*. Imagina-se que estes pacientes estejam mais suscetíveis a fazer um uso abusivo de drogas que aumentam a liberação dopaminérgica para atenuar o déficit dopaminérgico determinado pelo aumento de DAT. Até o momento, não encontramos na literatura nenhum trabalho que avalie concomitantemente o *status* do sistema dopaminérgico em pacientes com a comorbidade TDAH/uso de drogas, tampouco o efeito de MFD neste contexto.

Ao considerarmos os itens abaixo, parece-nos justificada a inclusão da neuroimagem no projeto original:

- independente da neuroimagem, trabalharemos com uma amostra de sujeitos com a comorbidade TDAH/uso de SPA que será tratada com MFD;
- o nosso grupo já vem trabalhando com neuroimagem no TDAH e agora dispõe de radiotracador especifico para realizar exames de neuroimagem molecular utilizados na literatura;
- há uma base neurobiológica em comum entre TDAH e uso de SPA, ainda pouco explorada;
- não encontramos nenhum estudo que trate deste assunto e/ou que apresente uma amostra de sujeitos como a aqui exposta.

Operacionalização da realização dos Spects:

Avaliaremos a densidade de DAT basal nos pacientes com a comorbidade TDAH/uso de SPA, ou seja, em todos os pacientes que entrarem no ECR descrito no projeto original e no adendo 1. Faremos um SPECT antes da intervenção medicamentosa (SPECT 1) e outro após 4 semanas, no fim do protocolo medicamentoso (SPECT 2).

O SPECT será realizado no Hospital de Clínicas de Porto Alegre, com o Serviço de Medicina Nuclear.

SPECT com [^{99m}Tc]-TRODAT-1:

Os SPECTs serão realizados em uma máquina GE Starcam 4000i, matriz 64X64, no Serviço de Medicina Nuclear do HCPA

Radiofármaco:

O TRODAT-1 será marcado com ^{99m}Tc de acordo com a técnica de desenvolvida por Kung et al., 2003 e Mosley et al., 2000. O ^{99m}Tc pertecnetato (Tco4+) será obtido de um Gerador de ^{99}Mo (^{99}Molebidenio) do Instituto de Pesquisa de Energia Nuclear (IPEN-SP) com eluição recente não mais de 24 hs. TRODAT-1 será obtido em forma de Kit do Laboratório do instituto de Energia Nuclear, Long-Tan, Taiwan (Republica Oriental da China – R.O.C.). O processo de marcação é simples, 60mCi de eluato de Tc-pertecnetato é injetado num frasco estéril contendo 5 ml de solução salina e se procede a re-esterilização e marcação submetendo o Kit a 16 atmosferas e temperatura de 120°C durante 30 minutos. Posteriormente, a solução de [99mTc]TRODAT-1 é esfriada em temperatura ambiente estando pronta para aplicação. A pureza radioquímica será determinada no Laboratório Medicina Nuclear do Hospital de Clínicas de Porto Alegre. Níveis superiores a 90% de pureza radioquímica serão exigidos para injeção do traçador.

Os níveis plasmáticos de [^{99m}Tc]TRODAT-1 permanecem estáveis durante o exame de SPECT, permitindo uma boa quantificação do DAT no corpo estriado através de imagem de SPECT (Mosley et al., 1998; Acton et al., 2000).

Procedimento:

A injeção intravenosa se efetuará sem restrição alimentar ou jejum. Depois da solução ter resfriado até a temperatura ambiente se injeta 2 ml contendo 25 mCi de [^{99m}Tc]TRODAT-1 numa veia periférica. Quatro horas após da injeção endovenosa se iniciará a aquisição de imagens na câmara de SPECT.

Os sujeitos deitarão numa maca com a cabeça apoiada num dispositivo especialmente desenhado no centro de rotação da câmara. Uma almofada será colocada debaixo dos joelhos e os braços serão apoiados ao lado do corpo para deixar os sujeitos mais relaxados e diminuir a movimentação.

Técnica de aquisição das imagens:

Para a aquisição SPECT colocando a janela de energia 140 Kev m uma largura de 15%. A matriz será de 128 x 128 usando uma órbita circular com movimentos 'step & shoot' com 64 passos de cada cabeça, onde o grau de rotação é de 360°. O tempo da aquisição por projeção é de 30 segundos com um fator de zoom 1.45 e ao término da aquisição se verifica o estudo no modo cine. Um sinograma será utilizado para controle de qualidade da presença de possíveis movimentos dos pacientes durante a aquisição. Em caso de movimento, deve se repetir à aquisição sem necessidade de efetuar nova injeção.

Processamentos das imagens SPECT:

A reconstrução das imagens de SPECT será obtida empregando um algoritmo de filtro retroprojeção filtrada e um filtro de corte Butterworth 0,45 "cut off" c/px de ordem 10. Imagens com matriz de aquisição de 128 x 128 serão obtidas e imagens tridimensionais em forma de cortes transaxiais, coronais e sagitais. Os algoritmos de correção de atenuação tendem a homologar a concentração nos núcleos basais à concentração no córtex cerebral (Kung et al., 1997).

Análise das imagens:

Para avaliação dos estudos SPECT com [^{99m}Tc]TRODAT-1 serão considerados os cortes transaxiais ao nível do corpo estriado (STR) e do cerebelo (CER), com espessura de corte de 3mm.

Para avaliação quantitativa dos DAT será calculado o potencial de ligação (PL), PL= [STR-OCC]/CER, onde STR representa a concentração de traçador no corpo estriado, e CER corresponde ao com ligação não específica. O cerebelo não contém neurônios dopaminérgicos e é utilizado como uma região sem ligação especifica (região de referência).

Análise estatística:

A comparação do potencial de ligação (PL) no corpo estriado entre os grupos se efetuará através de métodos de análise não paramétricos para amostras independentes (Teste de Mann-Whitney). Comparações entre grupos de voluntários sadios (controles) e pacientes portadores de DP e também se efetuarão através de um teste não paramétrico para amostras independentes (Teste de Mann-Whitney). Correlações entre as escalas de sintomas e o PL no corpo estriado será feita através do método de Spearman.

Aspectos Éticos e Proteção aos Direitos Humanos:

Todos os sujeitos receberão os esclarecimentos necessários sobre o projeto e, concordando com a participação, serão integrados ao protocolo após a assinatura do Termo de Consentimento Pós-Informação (anexo).

Os pesquisadores assumem, com os pacientes do projeto, um compromisso de sigilo das informações. Encerrada a participação no projeto, ofereceremos tratamento para o

TDAH no ambulatório do Programa de Déficit de Atenção (PRODAH), realizado na zona 7 do HCPA nas sextas-feiras, por cerca de dois meses e depois o paciente será encaminhado para a rede pública.

Os sujeitos serão submetidos ao SPECT em duas ocasiões. A preocupação existente refere-se a possíveis riscos envolvidos no procedimento, e a existência ou não de algum benefício direto aos sujeitos. A radiação oriunda do SPECT corresponde de 1/10 a 1/15 da radiação decorrente de Tomografia Computadorizada (TC) de Encéfalo. Em termos de exposição à radiação, o risco é inferior ao que se encontra com um exame rotineiramente feito, como a TC de encéfalo, ainda com a vantagem de não necessitar de contraste. Também, em função dos baixos riscos, este exame costuma ser utilizado em sujeitos hígidos, na categoria de controles, como por exemplo no estudo de Weng (2004), onde 40 sujeitos saudáveis foram submetidos ao SPECT com TRODAT.

Os potenciais riscos envolvidos no SPECT são:

- Punção venosa: pode acarretar incômodo aos sujeitos e, raramente, flebite;
- Exposição à radiação: a dose efetiva de radiação administrada a cada sujeito não ultrapassará o limite de 7 mSv, que é comparável ao grau de exposição em outros procedimentos diagnósticos de baixo risco, tais como o enema baritado. Tal nível de exposição à radiação encontra-se dentro dos limites recomendados pela Organização Mundial de Saúde (OMS) para sujeitos maiores que 18 anos dentro de projetos de pesquisa (entre 5mSv e 50mSv). Esta dose é consideravelmente mais baixa do que o limite anual de

exposição total a radiação recomendada pela OMS a indivíduos que participem de projetos de pesquisa.

O TRODAT-1 é um radiofármaco já em uso clínico em diversos países e tal produto já foi aprovado por U.S. Food & Drug Administration – FDA (IND# 56,623) dos Estados Unidos da América. O uso do TRODAT-1 está documentado em mais de 60 artigos científicos realizados em diversos países do mundo incluindo Europa, Ásia e Estados Unidos e publicado em revistas internacionais. Não há relato de reações adversas ou efeitos colaterais relativo ao uso do traçador. Outros centros de pesquisa em nosso país já utilizam o TRODAT, como por exemplo projeto já aprovado no comitê de ética em pesquisa da UNIFESP (CEP 0177/04, data 19/03/04). A utilização do TRODAT-1 tem um risco mínimo, já que a exposição à radiação é irrisória.

Serão adotadas as seguintes medidas de proteção e minimização dos riscos envolvidos na pesquisa:

- manejo dos materiais radioativos e dos rejeitos será feito de acordo com as normas da Comissão Nacional de Energia Nuclear (CNEM) por profissional capacitado.
- Apesar de das reações ao traçador serem muito improváveis, o acompanhamento pela equipe médica durante todo o procedimento facilita o diagnóstico precoce de eventuais reações alérgicas ao traçador e o tratamento precoce, minimizando o incômodo para os sujeitos.

- Flebite: um profissional altamente capacitado realizará a punção venosa com medidas de assepsia apropriadas; após o exame, tratamento das manifestações precoces da flebite através de explicação dos sinais iniciais do quadro.

Previsão de Custos/0rçamento:

a) Exames de neuroimagem: SPECTs.

Valor de cada exame = 94.90

Número total de exames = 80

Total= 7.592,00

b) Traçador TRODAT: Kit TRODAT-1 (INER, Taiwan)

Valor por paciente = R$ 300,00

Total para 80 exames = R$ 24.000,00

Valor total = 24.000,00 + 7592,00

O TRODAT será doado pelo LiNC – UNIFESP (Laboratório Interdisciplinar de Neuroimagem e Cognição da Universidade Federal de São Paulo), abatendo-se portanto R$ 24.000,00do orçamento.

O valor restante será fornecido pelo laboratório Novartis.

RERÊNCIAS BIBLIOGRÁFICAS:

1. Szobot CM, Ketzer C, Cunha RD, Parente MA, Langleben DD, Acton PD, Kapczinski F, Rohde LA. The acute effect of methylphenidate on cerebral blood flow in boys with attention-deficit/hyperactivity disorder. *Eur J Nucl Med Mol Imaging* 2003;30(3):423-6.

2. Szobot C, Roman T, Cunha R, Acton P, Hutz M, Rohde LA. Brain perfusion and dopaminergic genes in boys with attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2004 Sep 23;132B(1):53-58.

3. Rohde LA, Roman T, Szobot C, Cunha RD, Hutz MH, Biederman J. Dopamine transporter gene, response to methylphenidate and cerebral blood flow in attention-deficit/hyperactivity disorder: a pilot study. *Synapse*. 2003 May;48(2):87-9.

4. Roman T, Szobot C, Martins S, Biederman J, Rohde LA, Hutz MH. Dopamine transporter gene and response to methylphenidate in attention-deficit/hyperactivity disorder. Pharmacogenetics. 2002 Aug;12(6):497-9.

5. Lou HC, Henriksen L, Bruhn P, Borner H, Nielsen JB. Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch Neurol. 1989 Jan;46(1):48-52.

6. Zametkin AJ, Liebenauer LL, Fitzgerald GA, King AC, Minkunas DV, Herscovitch P, Yamada EM, Cohen RM. 1993. Brain metabolism in teenagers with attention-deficit hyperactivity disorder. Arch Gen Psychiatry; 50: 333-40.

7. Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, Sarfatti SE, Vauss YC, Snell JW, Lange N, Kaysen D, Krain AL, Ritchie

GF, Rajapakse JC, Rapoport J. 1996. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry 53: 607-16.

8. Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J. 1997. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 48: 589-601.

9. Semrud-Clikeman M, Steingard RJ, Filipek P, Biederman J, Bekken K, Renshaw PF. Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry. 2000 Apr;39(4):477-84.

10. Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, Castellanos FX. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. Neurology. 1998 Apr;50(4):1087-93.

11. Dresel S, Krause J, Krause KH, LaFougere C, Brinkbaumer K, Kung HF, Hahn K, Tatsch K. 2000. Attention deficit hyperactivity disorder: binding of [^{99m}Tc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. Eur J Nucl Med 27: 1518-1524.

12. Krause KH, Dresel SH, Krause J, Kung HF and Tatsch K. 2000. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography.

13. Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology. 2004a;47 Suppl 1:3-13.

14. Volkow ND, Fowler JS, Wang GJ, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. Mol Psychiatry. 2004b Jun;9(6):557-69.

15. Kung HF, Kung MP, Choi SR. Radiopharmaceuticals for single-photon emission computed tomography brain imaging. Semin Nucl Med. 2003;33(1):2-13.

16. Mozley, P.D., Schneider, J.S., Acton, P.D., Plossl K., Stern, M.B., Siderowf, A., Leopold N.A., Li, P.Y., Alavi,A., Kung, H.F. Binding of Tc99m Trodat-1 to Dopamine Transporters in Patients with Parkinson's Disease and in Healthy volunteers. J. Nucl. Med. 2000; 41: 584-589.

17. Mozley PD, Stubbs JB,Plossl,K., Dresel, S.H., Barraclough, E.D., Alavi,A., Araujo,L.I. Kung,H.K. Biodistribution and dosimetry of a Tc 99m labeled tropane to image dopamina transporters. J Nucl Med 1998. 39: 2069-2076

18. Acton PD, Meyer PT, Mozley PD, Plossl K, Kung HF. Simplified quantification of dopamine transporters in humans using [99mTc]TRODAT-1 and single-photon emission tomography. Eur J Nucl Med. 2000;27(11):1714-8.

19. Kung MP, Stevenson DA, Zhuang ZP, Vessotskie JM, Chumpradit S, Sun XM, Kung HF. Characterization of a novel iodinated ligand, IPMPP, for human dopamina D4 receptors in CHO cells. Life Sci 60:91-100, 1997.

20. Weng YH, Yen TC, Chen MC, Kao PF, Tzen KY, Chen RS, Wey SP, Ting G, Lu CS. Sensitivity and specificity of 99mTc-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. J Nucl Med. 2004 Mar;45(3):393-401.

HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE
Grupo de Pesquisa e Pós-Graduação
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

RESOLUÇÃO

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institucional Review Board (IRB0000921) analisaram o projeto:

Projeto: 03-319

Pesquisador Responsável:
FLAVIO PECHANSKY

Título: TRANSTORNO DE DÉFICIT/ATENÇÃO HIPERATIVIDADE E ABUSO DE SUBSTÂNCIAS EM ADOLESCENTES: ESTUDO SOBRE A SUA ASSOCIAÇÃO E SOBRE O EFEITO CEREBRAL ATRAVÉS DE SPECT, E CLÍNICO, DO TRATAMENTO FARMACOLÓGICO COM METILFENIDATO

Data da Versão:

TCLE SPECT 22/03/2005

Este documento referente ao projeto acima foi Aprovado em seus aspectos éticos e metodológicos, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde.

Porto Alegre, 22 de março de 2005.

Profª Nadine Clausell
Coordenadora do GPPG e CEP-HCPA

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

"Transtorno de Déficit de Atenção/Hiperatividade e abuso de substâncias em adolescentes: estudo sobre a sua associação e sobre o efeito cerebral, através de SPECT, e clínico, do tratamento farmacológico com metilfenidato".

Você está sendo convidado a participar de um estudo desenvolvido pela Universidade Federal do Rio Grande do Sul, Departamento de Psiquiatria, Programa de Transtorno de Déficit de Atenção/Hiperatividade (TDAH) e Centro de Pesquisas e Álcool e Drogas. Trata-se de um estudo a sobre o tratamento farmacológico do TDAH em adolescentes usuários de drogas. O TDAH é uma condição psiquiátrica que afeta a concentração, a atividade motora e o controle dos impulsos, acarretando em, por exemplo, distrações, esquecimentos, desorganização, mexer-se excessivamente e falar demais. Através deste estudo, analisaremos a resposta dos sujeitos ao remédio metilfenidato. Para participar desta fase do estudo, está implícito que você apresenta TDAH e também Abuso de drogas.

1. Quais são os meus direitos?

A sua participação é voluntária e você pode encerrar a sua participação no estudo no momento em que desejar. A nossa equipe assume um compromisso com você de absoluto sigilo das informações. Você tem o direito de não participar desta pesquisa. Também, uma vez participando desta pesquisa, você tem o direito de desistir a qualquer momento do estudo, se assim o desejar.

2. Qual a minha participação?

Você virá ao Hospital de Clínicas, em função deste protocolo, em cinco consultas ao longo de quatro semanas. Você responderá a algumas perguntas sobre sintomas psiquiátricos, aplicadas por membro de nossa equipe. Um de seus pais será questionado, na sua presença, sobre sintomas de TDAH e conversaremos individualmente com você sobre o seu uso de drogas e pediremos uma amostra da sua urina, para avaliar uso de maconha e cocaína.

Você receberá o metilfenidato, ou placebo, por quatro semana. Os comprimidos devem ser ingeridos três vezes ao dia, na dose de acordo com o seu peso.

Nem o médico que lhe entrega os remédios, nem você e sua família, saberão se você está recebendo placebo ou metilfenidato, ao longo das quatro semanas do protocolo. Mas, um outro membro do nosso grupo estará ao par da sua situação.

3. O que é o metilfenidato?

O metilfenidato é um remédio já bastante conhecido no meio científico. Já está comprovado que o metilfenidato é capaz de diminuir os sintomas desatenção (esquecimentos, distratibilidade, pouca concentração, etc.), a hiperatividade (mexer-se muito, pular de uma atividade para outra, falar demais) e a impulsividade (respostas precipitadas, interromper os outros) presentes no TDAH. É uma medicação segura e sem efeitos colaterais graves. Os principais efeitos colaterais são diminuição no apetite e insônia. Você receberá uma dose de acordo com o seu peso e com a sua tolerância.

4. O que é o Placebo?

O Placebo é um comprimido de apresentação idêntica ao metilfenidato, mas sem nenhum princípio ativo, ou seja, sem nenhum composto com ação farmacológica.

5. O que será feito com as minhas informações?

As suas informações são absolutamente sigilosos e serão repassadas a você mesmo.

Os seus resultados serão incluídos em um banco de dados (onde você será identificado por uma sigla) do nosso grupo, cujos resultados, em conjunto com os resultados de outros adolescentes, serão analisados. Ou seja, teremos resultados de um grupo de pacientes, sem identificação nominal ou que permita o reconhecimento pessoal dos integrantes, e é isto que eventualmente apresentaremos em ocasiões e publicações científicas, garantido o anonimato de sujeitos como você que aceitaram auxiliar neste estudo.

6. O que eu ganho participando deste estudo?

Você estará contribuindo com um estudo inédito em nosso meio, que poderá ajudar várias crianças e adolescentes em risco para uso de drogas.

Você também receberá uma avaliação psiquiátrica realizada por uma equipe com ampla experiência na saúde mental de crianças e de adolescentes.

Também, ao iniciar o tratamento com o metilfenidato, você estará iniciando o tratamento para um problema que você apresenta e que lhe traz prejuízos em sua vida, como nos estudos.

7. O que será feito quando acabar as quatro semanas do estudo?

Se você quiser, poderá ficar em atendimento com a nossa equipe por mais 2 meses. Após este período, você será encaminhado para a outros serviços de Saúde Mental da rede pública.

Você poderá entrar em contato, se necessário, entre as consultas, com o Dr. Flávio Pechansky ou com a Dra. Claudia M. Szobot através do telefone 51-3330-5813.

Declaro estar de acordo com os termos aqui expostos, aceitar participar deste estudo.

Sujeito número:

Nome completo:

Data de Nascimento:

Endereço:

Telefone:

Assinatura:

Nome completo do responsável:

Assinatura do responsável:

Assinatura do pesquisador:

ANEXO 4

INSTRUMENTOS

TRIAGEM NA COMUNIDADE/ Dados sócio-demográficos

Entrevistador:…….. Data:…….. … SIGLA:……..

(aplicado junto aos pais, após explicação dos objetivos da pesquisa)

(1) Caso (2) Controle (3) PC (4) excluído (5) não encontrado após 3 visitas; (6) TUSP álcool

Nome Completo:…….……..……Endereço:…….……

Telefone Residencial:……Celular:……Recados:……..….

Etnia: (1) branca (2) negra (3) mista (4) oriental **Idade entrevista:** (15) (16) (17) (18) (19) (20)

Escolaridade: último ano em que foi aprovado:

(0)analfabeto (1)primeira-série (2)segunda-série (3)terceira-série (4)quarta-série (5)quinta-série

(6) sétima-série (8)oitava série (9)primeiro ano segundo-grau (10)segundo ano segundo-grau

(11)terceiro ano segundo-grau (12)superior completo (13)mestrado/doutorado

Freqüentando a escola em 2004? (0)sim (1)não **Tem repetências:** (0)não (1)sim. Se sim: quantas e quais séries?

Pais biológicos: (0) ainda moram juntos (1) separados

Quem mora na casa? Listar todas as pessoas e idades:

a) 12 anos ou mais:

b) até 11 anos:

Total de dinheiro que a família recebe em um mês:

Escolaridade pai/padrasto:

(0) analfabeto (1)primeira-série (2)segunda-série (3)terceira-série (4)quarta-série (5)quinta-série

(6) sétima-série (8)oitava série (9)primeiro ano segundo-grau (10)segundo ano segundo-grau

(11)terceiro ano segundo-grau (12)superior completo (13)mestrado/doutorado

Escolaridade mãe/madrasta:

(0) analfabeto (1)primeira-série (2)segunda-série (3)terceira-série (4)quarta-série (5)quinta-série

(6) sétima-série (8)oitava série (9)primeiro ano segundo-grau (10)segundo ano segundo-grau

(11)terceiro ano segundo-grau (12)superior completo (13)mestrado/doutorado

Adolescente se considera praticante de alguma religião? (0)sim (1)não

Adolescente fez ou faz algum tratamento com psicólogo ou psiquiatra? (0)não (1)sim

CLASSIFICAÇÃO SÓCIO-ECONÔMICA ABIPEME

a) Instrução do chefe da família	ABIPEME
Analfabeto; primário incompleto (não completou a 4ª série do ensino fundamental)	0
primário completo; ginasial incompleto (não completou a 8ª série do ensino fundamental)	5
ginasial completo; colegial incompleto (não completou a 3ª série do ensino médio)	10
colegial completo; superior incompleto (iniciou, mas não terminou faculdade)	15
superior completo	21

Itens de conforto familiar - critério ABIPEME. Os pontos estão no corpo da tabela abaixo:

Itens de posse	**Não tem**	**Quantidade possuída**					
		1	**2**	**3**	**4**	**5**	**6 e+**
Automóvel		4	9	13	18	22	26
televisor em cores		4	7	11	14	18	22
Banheiro		2	5	7	10	12	15
empregada mensalista		5	11	16	21	26	32
rádio (excluindo o do carro)		2	3	5	6	8	9
máquina de lavar roupa		8	8	8	8	8	8
vídeo cassete		10	10	10	10	10	10
aspirador de pó		6	6	6	6	6	6
geladeira comum ou com freezer		7	7	7	7	7	7

Classes	Critério ABIPEME
A	89 ou +
B	59-88
C	35-58
C	20-34
E	0-19

Com o adolescente sozinho:

O que você gosta de fazer?

Qual a sua comida preferida?

Qual o seu refrigerante preferido?

Qual a sua bebida de álcool preferida?

Quantas horas de TV você assiste por dia?

Você está satisfeito com seu corpo?

Você tem alguém em quem confie, para conversar?

Você fuma nicotina (0) não (1)sim

Já experimentou nicotina? (0)não (1)sim. Idade da experimentação:……..

Quantos cigarros de nicotina fuma por dia? ……..

AGORA, VOU LHE FAZER MAIS ALGUMAS PERGUNTAS SOBRE O SEU CONTATO COM NICOTINA, E COM OUTRAS SUBSTÂNCIAS, OK?

Aplicação do ASSIST.

ASSIST 2.0

Alcohol Smoking and Substance Involvement Screening Test – ASSIST
-Teste para Triagem do Envolvimento com Fumo, Álcool e outras Drogas-

1-Na sua vida, qual(is) dessas substâncias você já usou? **(SOMENTE USO NÃO-MÉDICO)**	**NÃO**	**SIM**
a. Derivados do tabaco (cigarros, charuto, cachimbo, fumo de corda...)	0	1
b. Bebidas alcoólicas (cerveja, vinho, destilados como pinga, uísque, vodka, vermutes...)	0	1
c. Maconha (baseado, erva, haxixe...)	0	1
d. Cocaína, crack (pó, pedra, branquinha, nuvem...)	0	1
e. Estimulantes como anfetaminas ou ecstasy (bolinhas, rebites...)	0	1
f. Inalantes (cola de sapateiro, cheirinho-da-loló, tinta, gasolina, éter, lança-perfume,benzina...)	0	1
g. Hipnóticos/sedativos (remédios para dormir: diazepam, lorazepan, Lorax, Dienpax, Rohypnol).	0	1
h. Drogas alucinógenas (como LSD, ácido, chá-de-lírio, cogumelos...)	0	1
i. Opióides (heroína, morfina, metadona, codeína...)	0	1
j. Outras, Especificar:_____	0	1

2-Durante os três últimos meses, com que freqüência você utilizou essa(s) substância(s) que mencionou? **(PRIMEIRA DROGA, DEPOIS A SEGUNDA DROGA, ETC.)**	**Nunca**	**1 ou 2 vezes**	**mensalmente**	**semanalmente**	**Diariamente ou quase todo dia**
a. Derivados do tabaco (cigarros, charuto, cachimbo, fumo de corda...)	0	1	2	3	4
b. Bebidas alcoólicas (cerveja, vinho, destilados como pinga, uísque, vodka, vermutes...)	0	1	2	3	4
c. Maconha (baseado, erva, haxixe...)	0	1	2	3	4
d. Cocaína, crack (pó, pedra, branquinha, nuvem...)	0	1	2	3	4
e. Estimulantes como anfetaminas ou ecstasy (bolinhas, rebites...)	0	1	2	3	4
f. Inalantes (cola de sapateiro, cheirinho-da-loló, tinta, gasolina, éter, lança-perfume,benzina...)	0	1	2	3	4
g. Hipnóticos/sedativos (remédios para dormir: diazepam, lorazepan, Lorax, Dienpax, Rohypnol).	0	1	2	3	4
h. Drogas alucinógenas (como LSD, ácido, chá-de-lírio, cogumelos...)	0	1	2	3	4
i. Opióides (heroína, morfina, metadona, codeína...)	0	1	2	3	4
j. Outras, Especificar:_____	0	1	2	3	4

3- Durante os três últimos meses, com que freqüência você teve um forte desejo ou urgência em consumir? (PRIMEIRA DROGA, DEPOIS A SEGUNDA DROGA, ETC.)	**Nunca**	**1 ou 2 vezes**	**mensalmente**	**semanalmente**	**Diariamente ou quase todo dia**
a. Derivados do tabaco (cigarros, charuto, cachimbo, fumo de corda...)	0	1	2	3	4
b. Bebidas alcoólicas (cerveja, vinho, destilados como pinga, uísque, vodka, vermutes...)	0	1	2	3	4
c. Maconha (baseado, erva, haxixe...)	0	1	2	3	4
d. Cocaína, crack (pó, pedra, branquinha, nuvem...)	0	1	2	3	4
e. Estimulantes como anfetaminas ou ecstasy (bolinhas, rebites...)	0	1	2	3	4
f. Inalantes (cola de sapateiro, cheirinho-da-loló, tinta, gasolina, éter, lança-perfume,benzina...)	0	1	2	3	4
g. Hipnóticos/sedativos (remédios para dormir: diazepam, lorazepan, Lorax, Dienpax, Rohypnol).	0	1	2	3	4
h. Drogas alucinógenas (como LSD, ácido, chá-de-lírio, cogumelos...)	0	1	2	3	4
i. Opióides (heroína, morfina, metadona, codeína...)	0	1	2	3	4
j. Outras, Especificar:_____	0	1	2	3	4

4-Durante os três últimos meses, com que freqüência o seu consumo de (PRIMEIRA DROGA, DEPOIS A SEGUNDA DROGA, ETC.) resultou em problema de saúde, social, legal ou financeiro?	**Nunca**	**1 ou 2 vezes**	**mensalmente**	**semanalmente**	**Diariamente ou quase todo dia**
a. Derivados do tabaco (cigarros, charuto, cachimbo, fumo de corda...)	0	1	2	3	4
b. Bebidas alcoólicas (cerveja, vinho, destilados como pinga, uísque, vodka, vermutes...)	0	1	2	3	4
c. Maconha (baseado, erva, haxixe...)	0	1	2	3	4
d. Cocaína, crack (pó, pedra, branquinha, nuvem...)	0	1	2	3	4
e. Estimulantes como anfetaminas ou ecstasy (bolinhas, rebites...)	0	1	2	3	4
f. Inalantes (cola de sapateiro, cheirinho-da-loló, tinta, gasolina, éter, lança-perfume, benzina...)	0	1	2	3	4
g. Hipnóticos/sedativos (remédios para dormir: diazepam, lorazepan, Lorax, Dienpax, Rohypnol).	0	1	2	3	4
h. Drogas alucinógenas (como LSD, ácido, chá-de-lírio, cogumelos...)	0	1	2	3	4
i. Opióides (heroína, morfina, metadona, codeína...)	0	1	2	3	4
j. Outras, Especificar:_____	0	1	2	3	4

5-Durante os três últimos meses, com que freqüência, por causa do seu uso de (PRIMEIRA DROGA, DEPOIS A SEGUNDA DROGA, ETC.), você deixou de fazer coisas que eram normalmente esperadas de você?	**Nunca**	**1 ou 2 vezes**	**mensalmente**	**semanalmente**	**Diariamente ou quase todo dia**
a. Derivados do tabaco (cigarros, charuto, cachimbo, fumo de corda...)	0	1	2	3	4
b. Bebidas alcoólicas (cerveja, vinho, destilados como pinga, uísque, vodka, vermutes...)	0	1	2	3	4
c. Maconha (baseado, erva, haxixe...)	0	1	2	3	4
d. Cocaína, crack (pó, pedra, branquinha, nuvem...)	0	1	2	3	4
e. Estimulantes como anfetaminas ou ecstasy (bolinhas, rebites...)	0	1	2	3	4
f. Inalantes (cola de sapateiro, cheirinho-da-loló, tinta, gasolina, éter, lança-perfume, benzina...)	0	1	2	3	4
g. Hipnóticos/sedativos (remédios para dormir: diazepam, lorazepan, Lorax, Dienpax, Rohypnol).	0	1	2	3	4
h. Drogas alucinógenas (como LSD, ácido, chá-de-lírio, cogumelos...)	0	1	2	3	4
i. Opióides (heroína, morfina, metadona, codeína...)	0	1	2	3	4
j. Outras, Especificar:_____	0	1	2	3	4

6-Há amigos, parentes ou outra pessoa que tenha demonstrado preocupação com seu uso de (PRIMEIRA DROGA, DEPOIS A SEGUNDA DROGA, ETC...)**?**	**NÃO, nunca**	**SIM, mas não nos últimos 3 meses**	**SIM, nos últimos 3 meses**
a. Derivados do tabaco (cigarros, charuto, cachimbo, fumo de corda...)	0	1	2
b. Bebidas alcoólicas (cerveja, vinho, destilados como pinga, uísque, vodka, vermutes...)	0	1	2
c. Maconha (baseado, erva, haxixe...)	0	1	2
d. Cocaína, crack (pó, pedra, branquinha, nuvem...)	0	1	2
e. Estimulantes como anfetaminas ou ecstasy (bolinhas, rebites...)	0	1	2
f. Inalantes (cola de sapateiro, cheirinho-da-loló, tinta, gasolina, éter, lança-perfume, benzina...)	0	1	2
g. Hipnóticos/sedativos (remédios para dormir: diazepam, lorazepan, Lorax, Dienpax, Rohypnol...).	0	1	2
h. Drogas alucinógenas (como LSD, ácido, chá-de-lírio, cogumelos...)	0	1	2
i. Opióides (heroína, morfina, metadona, codeína...)	0	1	2
j. Outras, Especificar:_____	0	1	2

7-Alguma vez você já tentou controlar, diminuir ou parar o uso de (PRIMEIRA DROGA, DEPOIS A SEGUNDA DROGA, ETC...)**?**	**NÃO, nunca**	**SIM, mas não nos últimos 3 meses**	**SIM, nos últimos 3 meses**
a. Derivados do tabaco (cigarros, charuto, cachimbo, fumo de corda...)	0	1	2
b. Bebidas alcoólicas (cerveja, vinho, destilados como pinga, uísque, vodka, vermutes...)	0	1	2
c. Maconha (baseado, erva, haxixe...)	0	1	2
d. Cocaína, crack (pó, pedra, branquinha, nuvem...)	0	1	2
e. Estimulantes como anfetaminas ou ecstasy (bolinhas, rebites...)	0	1	2
f. Inalantes (cola de sapateiro, cheirinho-da-loló, tinta, gasolina, éter, lança-perfume, benzina...)	0	1	2
g. Hipnóticos/sedativos (remédios para dormir: diazepam, lorazepan, Lorax, Dienpax, Rohypnol).	0	1	2
h. Drogas alucinógenas (como LSD, ácido, chá-de-lírio, cogumelos...)	0	1	2
i. Opióides (heroína, morfina, metadona, codeína...)	0	1	2
j. Outras, Especificar:_____	0	1	2

8-Alguma vez você já usou drogas por injeção? (Apenas uso não- médico)	**NÃO, nunca**	**SIM, mas não nos últimos 3 meses**	**SIM, nos últimos 3 meses**
	0	1	2

Escore das questões 2.2 – 2.8

	Uso ocasional	**Sugestivo de abuso**	**Sugestivo de Dependência**
Tabaco	0-3	4-15	16-20
Álcool	0-3	4-15	16-20
Maconha	0-3	4-15	16-20
Cocaína	0-3	4-15	16-20
Anfetaminas	0-3	4-15	16-20
Inalantes	0-3	4-15	16-20
Sedativos	0-3	4-15	16-20
Alucinógenos	0-3	4-15	16-20
Opiáceos	0-3	4-15	16-20

MINI PARA ABUSO OU DEPENDÊNCIA DE ÁLCOOL E DROGAS:
PARA CONFIRMAÇÃO DE ASSIST POSITIVO

J. DEPENDÊNCIA / ABUSO DE ÁLCOOL

J1	Nos últimos 12 meses, por mais de três vezes você bebeu, em menos de três horas, mais do que cinco latas de cerveja ou uma garrafa de vinho ou três doses de uma bebida alcoólica forte (pinga, caipirinha, conhaque, vodka, whisky...)?	➔ NÃO	SIM	1

J2 **Durante os últimos 12 meses:**

a	Constatou que precisava de quantidades cada vez maiores de álcool para obter o mesmo efeito?	NÃO	SIM	2
b	Quando bebia menos, as suas mãos tremiam, transpirava ou sentia-se agitado (a)?			3
	Alguma vez bebeu uma dose para evitar esses problemas ou evitar uma ressaca?	NÃO	SIM	
	COTAR **"SIM"**, SE RESPOSTA **"SIM"** NUM CASO OU NO OUTRO			
c	Quando começava a beber, com freqüência bebia mais do que pretendia?	NÃO	SIM	4
d	Tentou, mas não conseguiu diminuir seu consumo de álcool ou parar de beber?	NÃO	SIM	5
e	Nos dias em que bebia, passava muito tempo procurando bebida, bebendo ou se recuperando dos efeitos do álcool?	NÃO	SIM	6
f	Reduziu suas atividades (lazer, trabalho, cotidianas) ou passou menos tempo com os outros por causa da bebida?	NÃO	SIM	7
g	Continuou a beber mesmo sabendo que isso lhe causava problemas de saúde ou problemas psicológicos?	NÃO	SIM	8

HÁ PELO MENOS **3 RESPOSTAS "SIM"** EM **J2?**

NÃO	**SIM**
DEPENDÊNCIA DE ÁLCOOL ATUAL	

J3 **Durante os últimos 12 meses:**

a	Ficou embriagado ou de "ressaca" várias vezes, quando tinha coisas para fazer no trabalho (/ na escola) ou em casa? Isso lhe causou problemas?	NÃO	SIM	9
	COTAR **"SIM"** SOMENTE SE A EMBRIAGUEZ / RESSACA CAUSOU PROBLEMAS			

→: **IR DIRETAMENTE** AO(S) QUADRO(S) DIAGNÓSTICO(S), **ASSINALAR NÃO** EM CADA UM E **PASSAR** AO MÓDULO SEGUINTE

b	Alguma vez esteve sob o efeito do álcool em situações em que isso era fisicamente arriscado como dirigir, utilizar uma máquina ou um instrumento perigoso... ?	NÃO	SIM	10
c	Teve problemas legais como uma interpelação ou uma condenação ou uma detenção porque tinha bebido?	NÃO	SIM	11
d	Continuou a beber mesmo sabendo que a bebida lhe causava problemas com seus familiares ou com outras pessoas?	NÃO	SIM	12

HÁ PELO MENOS **1 RESPOSTA "SIM"** EM **J3 ?**

NÃO	**SIM**
ABUSO DE ÁLCOOL **ATUAL**	

LISTA DE SUBSTÂNCIAS

ANFETAMINA	**ECSTASY**	**MORFINA**
BRANCA	**ERVA**	**ÓPIO**
CANNABIS	**ÉTER**	**PCP**
BASEADO	**GASOLINA**	**PÓ**
COCAÍNA	**HAXIXE**	**RITALINA**
CODEÍNA	**HEROÍNA**	**COGUMELO**
COLA	**L.S.D.**	**SPEEDS**
CRACK	**MARIJUANA**	**TEGISEC**
MACONHA	**MESCALINA**	**TOLUENO**
MERLA	**METADONA**	**TRICLOROETILENO**

➔: **IR DIRETAMENTE** AO(S) QUADRO(S) DIAGNÓSTICO(S), **ASSINALAR NÃO** EM CADA UM E **PASSAR** AO MÓDULO SEGUINTE

K. DEPENDÊNCIA / ABUSO DE SUBSTÂNCIAS (NÃO ALCOÓLICAS)

K1 Agora, vou lhe mostrar / ler (MOSTRAR A LISTA DAS SUBSTÂNCIAS / LER A LISTA ABAIXO) uma lista de drogas e de medicamentos e gostaria que me dissesse se, durante os últimos 12 meses, usou várias vezes uma destas substâncias para se sentir melhor, para mudar o seu estado de humor ou para ficar "de cabeça feita / chapado"?

➔ NÃO SIM

ENVOLVER COM UM CÍRCULO CADA SUBSTÂNCIA CONSUMIDA

Estimulantes : anfetaminas, "speed", ritalina, pílulas anorexígenas.
Cocaína: cocaína, "coca", crack, pó, folha de coca
Opiáceos: heroína, morfina, ópio, metadona, codeína, meperidina
Alucinogéneos: L.S.D., "ácido", mescalina, PCP, "pó de anjo", "cogumelos", ecstasy.
Solventes voláteis: "cola", éter.
Canabinóides: cannabis, "erva", maconha, "baseado", haxixe, THC
Sedativos: Valium, Diazepam, Lexotan, Lorax, Halcion, Frontal, Rohypnol, barbitúricos
Diversos: Anabolisantes, esteróides, "poppers". Toma outras substâncias?

ESPECIFICAR A(S) SUBSTÂNCIA (S) MAIS CONSUMIDA (S): _____

_____

ESPECIFICAR A(S) SUBSTÂNCIA (S) A SER(EM) EXPLORADA(S) SEGUNDO OS CRITÉRIOS ABAIXO INDICADOS:

- SE HÁ CONSUMO DE VÁRIAS SUBSTÂNCIAS (AO MESMO TEMPO OU SEQUENCIALMENTE):
  - CADA SUBSTÂNCIA (OU CLASSE DE SUBSTÂNCIAS) SEPARADAMENTE ☐
  - SOMENTE A SUBSTÂNCIA (OU CLASSE DE SUBSTÂNCIAS) MAIS CONSUMIDA ☐
- SE HÁ CONSUMO DE UMA SÓ SUBSTÂNCIA (OU CLASSE DE SUBSTÂNCIAS): ☐
  - SOMENTE UMA SUBSTÂNCIA (OU CLASSE DE SUBSTÂNCIAS)

K2 **Considerando o seu consumo de [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA], durante os últimos 12 meses:**

a Constatou que precisava de quantidades cada vez maiores de [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA] para obter o mesmo efeito? NÃO SIM 1

b Quando usava menos ou parava de consumir [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA], tinha problemas como dores, tremores, febre, fraqueza, diarréia, náuseas, suores, aceleração do coração, dificuldade de dormir ou sentir-se agitado(a), ansioso (a), irritável ou deprimido (a)?
Ou você tomava qualquer outra coisa para evitar esses problemas ou para se sentir melhor? NÃO SIM 2

COTAR **"SIM"**, SE RESPOSTA **"SIM"** NUM CASO OU NO OUTRO

c Quando começava a usar [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA], freqüentemente consumia mais do que pretendia? NÃO SIM 3

d Tentou, sem conseguir, diminuir ou parar de usar [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA]? NÃO SIM 4

e Nos dias em que usava [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA], passava mais de 2 horas tentando conseguir a(s) droga(s), se drogando, ou se recuperando dos efeitos do(a) [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA], ou ainda pensando nessas coisas? NÃO SIM 5

➔: **IR DIRETAMENTE** AO(S) QUADRO(S) DIAGNÓSTICO(S), **ASSINALAR NÃO** EM CADA UM E **PASSAR** AO MÓDULO SEGUINTE

f Reduziu as suas atividades (lazer, trabalho, cotidianas) ou passou menos tempo com os outros por causa da(s) droga(s)? NÃO SIM 6

g Continuou a usar [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA] mesmo sabendo que esta(s) lhe causava(m) problemas de saúde ou problemas psicológicos? NÃO SIM 7

HÁ PELO MENOS **3 RESPOSTAS "SIM"** EM **K2 ?**

ESPECIFICAR A(S) SUBSTÂNCIA(S): _____

NÃO SIM

***DEPENDÊNCIA DE SUBSTÂNCIAS(S)* ATUAL**

O (A) ENTREVISTADO(A) APRESENTA UMA DEPENDÊNCIA DE UMA/ VÁRIAS SUBSTÂNCIA(S) CONSUMIDA(S)? ➔

NÃO SIM

K3 **Durante os últimos 12 meses:**

a Por várias vezes ficou intoxicado ou "de cabeça feita / chapado" com [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA], quando tinha coisas para fazer no trabalho (/ na escola) ou em casa? Isso lhe causou problemas? NÃO SIM 8

COTAR "SIM" SOMENTE SE A INTOXICAÇÃO CAUSOU PROBLEMAS

b Alguma vez esteve sob o efeito de [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA] em situações em que isso era fisicamente arriscado como dirigir, utilizar uma máquina ou um instrumento perigoso, etc.? NÃO SIM 9

c Teve problemas legais como uma intimação ou uma condenação ou uma detenção porque tinha usado [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA]? NÃO SIM 10

d Continuou a usar [SUBSTÂNCIA OU A CLASSE DE SUBSTÂNCIAS SELECCIONADA] mesmo sabendo que esta(s) droga(s) lhe causava(m) problemas com os seus familiares ou com outras pessoas? NÃO SIM 11

HÁ PELO MENOS **1 "SIM"** EM **K3 ?**

ESPECIFICAR A(S) SUBSTÂNCIA(S): _____

NÃO **SIM**

ABUSO DE SUBSTÂNCIAS(S) ATUAL

CLINICAL GLOBAL ASSESSMENT SCALE

ESCALA DE AVALIAÇÃO GLOBAL DE CRIANÇAS

Considere o funcionamento psicológico, social e escolar da criança/adolescente numa linha hipotética contínua de saúde – doença mental.

Pontue de acordo com a sua visão do funcionamento real da criança/adolescente, independente de tratamento ou prognóstico. Os exemplos dados de comportamento são somente ilustrativos, não são, portanto, necessários para qualquer pontuação particular.

Use níveis intermediários (por exemplo: 35, 82, 58).

Período de tempo Especificado: 1 mês

Escore

100-91 – Funcionamento superior em todas as áreas (em casa, na escola, com os amigos); a criança/adolescente está envolvida numa grande variedade de atividades e tem muitos interesses (por exemplo, tem passatempos, participa em atividades fora do colégio, participa de organizações ou grupos como escoteiros, grupo da igreja, etc.); estimado, confiante; consegue lidar com as preocupações do dia-a-dia; bem na escola; sem sintomas.

90-81 – Bom funcionamento em todas as áreas: seguro na família, escola e com amigos. Podem existir dificuldades transitórias e preocupações do dia-a-dia com as quais tem, ocasionalmente, dificuldade em lidar (por exemplo, ansiedade leve associada a uma prova importante, "explosões" ocasionais com irmãos, pais ou amigos).

80-71 – Não mais do que prejuízo leve no funcionamento em casa, na escola ou com amigos; alguma alteração de comportamento ou angústia emocional pode estar presente em resposta a problemas da vida (por exemplo, separação dos pais, morte, nascimento de irmão), mas estas alterações duram pouco e o prejuízo na vida da criança também dura pouco; estas crianças/adolescentes são vistas pelos outros como causando uma perturbação mínima e não são consideradas problemáticas por quem as conhece.

70-61 – Alguma dificuldade numa única área, mas funcionando geralmente bastante bem (por exemplo, atos anti-sociais uma vez que outra ou isolados, como sacanagens ou roubos sem grande valor de vez em quando; dificuldades menores, mas constantes, com os deveres escolares; variações de humor de duração curta, medos e ansiedades que não implicam em comportamento evitativo grosseiro; dúvidas sobre si mesmo); têm algumas relações significativas com pessoas (amigos; familiares); a maioria das pessoas que não conhecessem esta criança/adolescente não a/o considerariam problemático(a), mas aqueles que realmente a/o conhecem bem, podem expressar preocupação.

60-51 – Funcionamento variável com dificuldades uma vez que outra ou sintomas em várias, mas não em todas as áreas sociais; perturbações podem ser enxergadas por aqueles que encontram a criança/adolescente num ambiente ou momento disfuncional, mas não para aqueles que vêm a criança/adolescente em outros ambientes.

50-41 – Grau moderado de problemas no funcionamento na maioria das áreas sociais ou prejuízo grave do funcionamento em uma área, como pode resultar de, por exemplo, presença de preocupações e idéias repetidas suicidas, recusa a ir a escola e outras formas de ansiedade, rituais, queixas físicas por "nervoso" (sem causa médica), ataques de ansiedade freqüentes, capacidades de relacionamento pobres e inapropriadas, episódios freqüentes de comportamentos agressivos ou anti-sociais com alguma manutenção de relações sociais significativas (com amigos; família; vizinhos).

40-31 – Prejuízo importante no funcionamento em várias áreas e incapacidade para funcionar em uma destas áreas, ou seja, perturbação em casa, na escola, com companheiros ou na sociedade em geral, por exemplo, agressão constante sem clara provocação; marcadamente retirado e com comportamento isolado, devido à perturbação no humor ou no pensamento; tentativa de suicídio com ou sem intenção de morrer; estas crianças/adolescentes provavelmente necessitem escola especial e/ou hospitalização ou retirada da escola (entretanto, este último critério não é suficiente para inclusão nesta faixa).

30-21 – Incapaz de funcionar em quase todas as áreas, por exemplo, fica em casa, numa sala, ou na cama todo o dia sem tomar parte em atividades sociais, ou prejuízo grave no contato com a realidade, ou prejuízo grave na comunicação (por exemplo, as vezes fala coisas que não têm nada haver com a ocasião ou com o assunto; não emenda um assunto no outro).

20-11 – Necessita considerável supervisão para prevenir que machuque os outros ou a si mesmo (por exemplo, freqüentemente violento, tentativas de suicídio repetidas), ou para manter a higiene pessoal, ou prejuízo grosseiro em todas as formas de comunicação, por exemplo, anormalidades graves na fala e nos gestos, marcada indiferença social, desligado do mundo, etc.

10-1 – Necessita supervisão constante (cuidados 24 horas) devido a comportamento gravemente agressivo ou auto-destrutivo ou prejuízo grave no contato com a realidade, na fala e no pensamento, no afeto ou na higiene pessoal.

Escore: _____

MTA SNAP – IV Escala de pontuação para pais e professores

Nome:.....Sexo:.....Idade:.....Escolaridade:..... Etnia:.....
Avaliado por:.....Tipo de Classe:.....Tamanho da Classe:.....

Para cada item, marque a coluna que melhor descreve esta criança:

	NEM UM POUCO	UM POUCO	BASTANTE	DEMAIS
1. Não consegue prestar muita atenção a detalhes ou comete erros por descuido nos trabalhos da escola ou tarefas.				
2. Tem dificuldades de manter atenção em tarefas ou atividades de lazer.				
3. Parece não estar ouvindo quando se fala diretamente com ele.				
4. Não segue instruções até o fim e não termina deveres de escola, tarefas ou obrigações.				
5. Tem dificuldades para organizar tarefas e atividades.				
6. Evita, não gosta ou se envolve contra a vontade em tarefas que exigem esforço mental prolongado.				
7. Perde coisas necessárias para atividades (p.ex: brinquedos, deveres da escola, lápis ou livros).				
8. Distrai-se com estímulos externos.				
9. É esquecido em atividades do dia-a-dia.				
10. Mexe com as mãos ou os pés ou se remexe na cadeira.				
11. Sai do lugar na sala de aula ou em situações em que se espera que fique sentado.				
12. Corre de um lado para o outro ou sobe demais nas coisas em situações em que isto é inapropriado.				
13. Tem dificuldade em brincar ou envolver-se em atividades de lazer de forma calma.				
14. Não para ou freqüentemente está “a mil por hora”.				
15. Fala em excesso.				
16. Responde as perguntas de forma precipitada antes delas terem sido terminadas.				
17. Tem dificuldade de esperar sua vez.				
18. Interrompe os outros ou se intromete (p.ex: mete-se nas conversas / jogos).				
19. Descontrola-se.				
20. Discute com adultos.				
21. Desafia ativamente ou se recusa a atender pedidos ou regras de adultos.				
22. Faz coisas de propósito que incomodam outras pessoas.				
23. Culpa os outros pelos seus erros ou mau comportamento.				
24. É irritável ou facilmente incomodado pelos outros.				
25. É raivoso e ressentido.				
26. É rancoroso ou vingativo.				

INVENTÁRIO DE USO DE DROGAS

(1) Internação voluntária (2) Internação psiquiátrica involuntária (3) fazenda (4) ambulatório (5) medicação. Qual? Tratamentos recebidos:

	idade	quantia	Freqüência	Períodos de abstinência	contexto	Dias de consumo último mês
álcool	**Início:** **Fim:**				**%sozinho** **% amigos**	
maconha	**Início:** **Fim:**					
Cocaína aspirada	**Início:** **Fim:**					
crack	**Início:** **Fim:**					
solventes	**Início** **Fim:**					

MINI

	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**INÍCIO**	**TEMPO**
Depend. álcool										
Abuso Álcool										
Depend. Maconha										
Abuso Maconha										
Depend. Cocaína										
Abuso Cocaína										
Depend. *crack*										
Abuso *crack*										
Depend. *solventes*										
Abuso *abuso solventes*										

ESCALA DE AVALIAÇÃO DE EFEITOS COLATERAIS

DE MEDICAÇÕES ESTIMULANTES

INSTRUÇÕES

Por favor, pontue cada comportamento de 0 (ausente) até 9 (grave). Circule somente um número ao lado de cada item. Um zero significa que você não tem visto o comportamento nesta criança durante a última semana, e um 9 significa que você tem notado o comportamento e acredita que ele seja ou muito grave ou ocorra muito freqüentemente.

Comportamento	**Ausente**									**Sério**
Insônia ou dificuldade para dormir	0	1	2	3	4	5	6	7	8	9
Pesadelos	0	1	2	3	4	5	6	7	8	9
Fica com olhar perdido ou sonha acordado	0	1	2	3	4	5	6	7	8	9
Fala menos com os outros	0	1	2	3	4	5	6	7	8	9
Desinteressado pelos outros	0	1	2	3	4	5	6	7	8	9
Apetite diminuído	0	1	2	3	4	5	6	7	8	9
Irritável	0	1	2	3	4	5	6	7	8	9
Dores de estômago	0	1	2	3	4	5	6	7	8	9
Dores de cabeça	0	1	2	3	4	5	6	7	8	9
Sonolência	0	1	2	3	4	5	6	7	8	9
Triste / Infeliz	0	1	2	3	4	5	6	7	8	9
Chora fácil	0	1	2	3	4	5	6	7	8	9
Ansioso	0	1	2	3	4	5	6	7	8	9
Rói as unhas	0	1	2	3	4	5	6	7	8	9
Eufórico / Feliz fora do comum	0	1	2	3	4	5	6	7	8	9
Tontura	0	1	2	3	4	5	6	7	8	9
Tiques ou movimentos de nervoso	0	1	2	3	4	5	6	7	8	9

CGI – 1 (GRAVIDADE) [apenas na consulta inicial]

Considerando sua experiência clínica, como você avalia o <u>estado mental</u> deste paciente <u>neste momento</u>?

0	*Não avaliado*	
1	*Normal*	(ausência de sintomas)
2	*Estado borderline*	(duvidosa, transitória ou sem prejuízo funcional)
3	*Levemente doente*	(prejuízo funcional leve)
4	*Moderadamente doente*	(desempenha atividades com esforço)
5	*Acentuadamente doente*	(sintomas intensos, desempenho limitado)
6	*Gravemente doente*	(consegue desempenhar praticamente só com assistência)
7	*Extremamente doente*	(desempenho completamente comprometido)

CGI – 2 (MELHORA CLÍNICA) [para as consultas de seguimento]

0	*Não avaliado*
1	*Muito melhor*
2	*Melhor*
3	*Pouco melhor*
4	*Não houve mudança*
5	*Pouco pior*
6	*Pior*
7	*Muito pior*

CGI-3 (EFICÁCIA) [para as consultas de seguimento]

EFEITOS TERAPÊUTICOS	*EVENTOS ADVERSOS*			
	Nenhum	*Não interfere com as atividades do paciente*	*Interfere significativamente com as atividades do paciente*	*Superam os efeitos terapêuticos*
NOTÁVEIS: melhora importante, quase completa remissão dos sintomas	*01*	*02*	*03*	*04*
MODERADOS: remissão parcial dos sintomas	*05*	*06*	*07*	*08*
MÍNIMOS: discreta melhora, não alterou o estado do paciente	*09*	*10*	*11*	*12*
INALTERADO OU PIOR	*13*	*14*	*15*	*16*
NÃO AVALIADO	*00*			

Reconsultas protocolo medicamentoso (em cada uma das 6 consultas):

a) aderência/ embalagem de pílulas
b) SNAP
c) CGI
d) Barkley
e) Uso de drogas na semana (sozinho com adolescente):

	domingo	segunda	terça	quarta	quinta	sexta	sábado
Álcool: bebida e qtidade; porres?							
Maconha: Quantidade							
Cocaína aspirada							
crack							
solventes							
Outra?							