Pharmacological Cognitive Enhancers in Children and Adolescents

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Background
Cognitive impairment is evident in a variety of pediatric neuropsychiatric disorders, including Attention deficit/hyperactivity disorder (ADHD), traumatic brain injury, mood disorders, autistic spectrum disorders, early onset schizophrenia, and congenital central nervous system disorders such as cerebral palsy.1 Pharmacological cognitive enhancement involves the use of pharmaceutical products or newer technologies to improve aspects of thought and behavior; thus leading to better performance on mental tasks, enhanced alertness and ability to sustain heightened mental activity. Pharmacological cognitive enhancers (PCEs) are medications which improve cognitive functions such as attention, working memory, learning, and executive function; as a result, they lead to better performance in the classroom as well as in social settings.2 One of the best illustrations of this concept has been the successful and widely prevalent use of psychostimulants to treat the core symptoms of ADHD. A substantial body of literature and research supports their clinical use. Evidence that the psychostimulants improve cognitive performance has been a more recent development; however such data is growing, especially based on a newer paradigm suggesting a hypofunction of different regions of the prefrontal cortex is the unifying concept underlying ADHD.3

The use of PCEs with other neuropsychiatric disorders in children is a relatively newer field in terms of the ongoing research to establish safety and efficacy. Children with traumatic brain injury may benefit from the use of cholinesterase inhibitors such as donepezil to improve measures of cognition such as sustained attention and learning.4 D-Cycloserine has been shown to reduce social withdrawal in autistic children, and may have other positive effects on cognition as well.5 Modafinil, a wakefulness promoting agent has been shown to improve facial recognition in patients during their first episode of schizophrenia, a finding that may have applicability to the pediatric population suffering from psychosis and autism.6 Youth with neuropsychiatric disorders are a population in need of well designed treatment strategies aimed at improving their cognitive function.

There is evidence that the use of pharmacologic cognitive enhancers is growing among the ‘cognitively healthy.’ In one survey, up to 16% of college students reported the use of stimulants during the previous year. In a 2005 survey by the U.S. National Institute on Drug Abuse, 2.5 % of 13-14 year olds, 3.4 % of 15-16 year olds, and 5.1 % of 17-18 year olds used methylphenidate illicitly. Although some of this use can be termed recreational, a substantial majority use PCE’s to help them in the classroom. Nearly 90% of modafinil use is by healthy, non-sleep deprived individuals, such as physicians, academics, and students.7,8 It is clear, therefore, that the use of PCE’s by the healthy is becoming a societal issue that demands the attention of public officials and the neuroscience community.

The field of neuroethics, a subfield within biomedical ethics, has arisen to address the complex ethical issues that arise when findings from the burgeoning research in neuroscience are carried into medical practice; and subsequently into public attention.9 The potential benefit from these drugs by those with disorders such as ADHD, traumatic brain injury, autism, and other disorders seems to be very clear: Less so is the use of PCEs by the ‘healthy,’ for the purpose of enhancing cognition and increasing productivity. Neuroethics seeks to answer some of the difficult questions that arise from such use, both
Ethical Issues in Cognitive Enhancement

The issue of cognitive enhancement can be addressed on an individual as well as societal level. A useful framework would be to examine the issue from the point of view of the four central principles of biomedical ethics: Autonomy, Beneficence, Non-Maleficence, and Justice.

Autonomy:
Autonomy refers to a person’s right to choose or decline a particular intervention based on its perceived benefits as well as risks. With respect to youth, this is modified by the fact that treatment decisions are made by the parents or guardians who are trusted to act in the best interests of their children. This reduction in autonomy is ethically permissible in light of the fact that society accepts the right of parents to compel children to do other things they may be unwilling to do, such as eat their vegetables or go to bed by a certain time to assure adequate rest. In healthy individuals, the issue of autonomy with respect to PCEs is somewhat more complex. Youth that use PCEs for cognitive enhancement may be under increased pressure to take medications from peers or other sources. There can be an element of coercion in a decision such as this, especially if use became more prevalent. Currently, prescribing stimulants for non-medical use is illegal and subject to substantial penalties. However, other PCEs such as modafinil can be prescribed for such conditions as ‘jet-lag’ to healthy individuals seeking this medication for cognitive enhancement. It is therefore possible to envision a situation when young individuals could feel compelled to take PCEs to ‘keep up’ in an academic environment where such use is common, if not widespread. In such an environment, the decision to opt out may potentially produce diminished opportunities in education and, later, possibly in the job market. This coercive milieu can certainly threaten autonomy in children and adolescents who may be very responsive to peer-pressure and competition.

Beneficence:
Beneficence is defined as the responsibility of the physician to the patient to act in the best interests of such an individual. This concept is applicable to the concerns of society as well. Children with ADHD and other neuropsychiatric disorders clearly benefit from medical intervention aimed at improving their cognitive performance. In individuals with ADHD, for example, treatment with methylphenidate may allow a person to successfully graduate from high school or college, and hold a job; their function and the outcome may be jeopardized by a lack of or inadequate treatment of this disorder. Likewise, an effective intervention with a patient with brain injury may prevent institutionalization and improve quality of life for the patient and his family. Thus, children and adolescents with certain neuropsychiatric disorders have a right to receive effective treatment directed at improving their cognitive and social functioning.

Society at large benefits from the use of PCEs by those with cognitive impairment in terms of the potential contributions to the workforce, reductions in costs related to unemployment, reduction in the costs related to automobile and other accidents. There is
also the tangible benefit of knowing that the inequalities imposed by neuropsychiatric disease are ameliorated by effective medical intervention.

In contrast, the use of PCEs by healthy individuals may create moral and ethical dilemmas. Such individuals receive benefit from PCEs by virtue of having improved mental skills, enhanced ability to work and improved alertness when tired. Specifically, professionals such as surgeons, air traffic controllers, and military personnel who must maintain high levels of alertness and mental proficiency for long periods may benefit from PCE use.10 This benefits the public for obvious reasons, such as improved medical care and a safer and more secure place in which to live. However, the use of PCEs by the healthy can also have possible adverse effects on health, especially in the long term. For example, the psychostimulants may have possible cardiac risks as well as those on weight and appetite. There is also the significant looming risk of dependence and addiction. These risks are acceptable when treating individuals with ADHD for example, but may be less so in terms of PCE use by the healthy. Finally, there is a concern that some individuals seeking the benefits from the use of PCE's can, in fact, overestimate the benefit conveyed and place themselves or others at risk. This concern is based on evidence that PCE’s can only compensate so much, and that there are limits to their effectiveness.

For several reasons, the use of PCEs by students is an issue of significant concern to those who work with children and adolescents. First, as stated above, there may be underlying medical problems, which increase the risk to those taking PCEs illicitly. Although less likely, there is also the possibility that such drugs may have an unforeseen effect on the developing “healthy” nervous system. Psychostimulants have been studied extensively in children with ADHD, but not as much is known about the long term effects on the “healthy” brain. Neuroscientists are concerned about subtle changes in mental functioning over time, which may result from pharmacological tinkering of the immature brain. This may amount to remembering too much detail or focusing too intently on a particular problem, perhaps reflecting a change in cognitive style. Acceptance of the use of PCEs to achieve academic and career goals may also detract from the psychological rewards that arise from one’s accomplishments. This may lead to increased disillusionment and dissatisfaction. Finally, there is the issue of whether taking PCEs is, in fact, cheating. For example, in an athletic competition such as the Olympics, athletes are routinely tested for banned substances such as anabolic steroids, as well as stimulants, which unquestionably can influence athletic performance and lead to better performance. There are many who believe these same standards should be applied in the classroom and boardroom, at least among those without a disorder such as ADHD, in order to eliminate unfair advantage.

**Non-maleficence:**
The principle of non-maleficence as it applies to the use of PCEs addresses the issue of “First Do No Harm”. The physician has an obligation to the patient to avoid a medication or course of therapy that would result in harm, either injury or death. It is unethical and illegal to prescribe a stimulant to a patient without an appropriate diagnosis. There is simply not enough known about the long term effects of PCEs in children and teens to support their routine use except for individuals with ADHD. In cases of other neuropsychiatric disorders, the treating clinician may decide that the potential benefit of a medical intervention
outweighs the risks. Physicians vary in their willingness to consider cognitive enhancing therapies such as modafinil in adults. There are some who view such use in non-impaired patients as ethically equivalent to a plastic surgeon using surgical techniques to enhance a patient’s appearance. There is also the possibility of unintentionally introducing a substance use disorder in an otherwise healthy person, by using PCEs. Some of the PCEs may increase dopamine in the nucleus accumbens, an effect that may theoretically increase the potential for drug seeking behavior and lead to chemical abuse and dependence. Finally, physicians who are willing to prescribe PCEs to the healthy should be aware of the fact that there are no randomized trials designed to investigate the long term effects of PCEs on this population.

**Justice:**

The principle of justice in ethics applies to the question of whether a treatment such as cognitive enhancement can be widely available to the population. Certainly, there are economic barriers to such treatment, for example, the average cost of a modafinil tablet is $6, and it is very unlikely that insurance would cover this cost. Furthermore, new pharmaceutical agents that aid in cognitive function will very likely be quite expensive and out of the reach of most people. Thus PCEs are available only to those with the means to pay for it, leading to a widening gulf in the distribution of such treatments and the means to acquire it. In addition, PCEs are not a form of medical treatment essential to life in the same way as, for example, insulin is for diabetes mellitus, or coronary artery bypass for heart disease. The patients who are in the best position to benefit from PCEs are children and adolescents with ADHD and other neuropsychiatric disorders, who have access to such treatments despite economic adversity through public insurance programs such as Medicaid. The use of PCEs in this population illustrates the principle of justice, namely that the ones who most need the care are getting it.

In summary there is growing discussion and debate in the neuro-scientific community regarding the issue of pharmacological cognitive enhancers. There is no question that these agents are pivotal in treating those with ADHD, especially in children and adolescents who need them to learn and succeed in the classroom and potentially avoid a variety of negative outcomes that follows untreated ADHD including school failure and drop-out, substance abuse, secondary anxiety and depressive disorders, and accidents. While the evidence for the use of PCE’s in other disorders is growing, more research needs to be done in this area to establish safety and efficacy. Use of PCEs in healthy individuals is another issue that touches on many ethical concerns. Whether these medications introduce unforeseen risks in the healthy is but one of these. For this reason, some leaders in the field of neuroethics advocate the teaching of this subject in academic programs where these issues are likely to be raised, such as neuroscience graduate programs, as well as graduate medical education programs in psychiatry and neurology. Given the fact that currently, there may be many novel agents in development which hold the promise of improved cognition in those with and without neuropsychiatric dysfunction, this is an appropriate and timely recommendation.

**Addendum: Indications for use in Children and Adolescents**
Attention Deficit hyperactivity disorder affects 3-7% of children worldwide and is the most common neuropsychiatric disorder affecting youth less than 18 years of age. It leads to both academic and psychosocial impairment as well as increased incidence of psychiatric co-morbidities such as major depressive disorder, oppositional defiant disorder, and anxiety disorders. There is a further increased risk of negative life outcomes such as early dropping out from education, substance abuse, and criminal activity in patients with ADHD. There is also the risk of accidental injury and death resulting from inattention and impulsive decision making. The psychostimulant medications include immediate and long acting formulations of methylphenidate and amphetamine salt as well as the more recently available prodrug: lisdexamphetamine (Vyvanse), and dexmethylphenidate. These medications clearly help ameliorate the core symptoms of hyperactivity, impulsivity, and inattention making it possible for patients to concentrate in school and learn.

Psychostimulant medications are thought to work by addressing the structural and biochemical alterations such as dysfunction in fronto-striatal neurocircuitry and dysfunction in norepinephrine (NA) and dopamine (DA) pathways leading to impairments in cognitive function. Specifically, working memory and executive function are affected leading to poor auditory processing and planning.

Atomoxetine is a non-stimulant medication approved for use in children and adolescents with ADHD, which blocks the re-uptake of NA in the prefrontal cortex and improves many of the symptoms of ADHD. In comparison to the stimulants, it has been shown to have a smaller effect size, however in carefully selected patients it has demonstrated effectiveness. In research settings an acute dose of atomoxetine has improved response inhibition in children with ADHD as well as healthy control subjects. The alpha2 agonists: clonidine and guanfacine are approved for ADHD and show effects on hyperactivity, impulsivity, and some cognitive tasks. Guanfacine has been shown to improve working memory and executive function in patients with ADHD but not in healthy controls.

Other applications of PCE’s in children and adolescents are currently being investigated with varying results. As mentioned above, Donepezil, a cholinesterase inhibitor used in the treatment of Alzheimer’s disease and other dementias has been investigated in patients with traumatic brain injury. In one literature review, there were three positive trials and one negative trial, all of which used cognitive function as the primary outcome measure. Modafinil has been shown to improve visuospatial planning and other measures of executive function in both subjects with ADHD and healthy controls. It is clear that more research is needed to examine the issue of cognitive enhancement in children and adolescents with neuropsychiatric dysfunction.

References

This is a review article and introduction to the neuroethical implications of the use of pharmacologic cognitive enhancing agents in youth. The article examines the use of medications widely employed in the treatment of cognitive difficulties encountered by those with Attention Deficit Hyperactivity disorder, traumatic brain injury, and severe mental illnesses. Cognitively healthy individuals who are seeking a competitive edge in
the classroom and professional settings are increasingly using these agents. The evidence supporting such use is discussed in light of the far-reaching societal issues that this raises.

This review article presents the present state of thought and discussion around the issues raised by the use of PCE’s among the cognitively healthy. Substantive evidence points to increasing use in the last decade. The implications of the use of PCE’s are examined. The authors suggest that there is inadequate knowledge regarding the use of PCE’s by the healthy, and that more research is needed to address the concerns and questions raised. This would help to facilitate discussion between neuroscientists and neuroethicists regarding the proper use of these agents. The authors also suggest that there are non-pharmacologic ways to enhance cognitive performance such as exercise and education.

3. Stahl S. Essential Psychopharmacology. Third ed. Cambridge University Press. 2008. This book brings together the knowledge derived from advances in neurobiological research with clinical knowledge to clearly explain the central concepts used in the pharmacologic treatment of psychiatric disorders. Extensive graphics and illustrations are used to enliven the concepts and enhance understanding, hopefully leading to improved care of patients. This is a comprehensive course in the theoretical concepts in neuroscience that provide the basis for psychopharmacologic practice, and is in wide use amongst researchers and clinicians alike.

This study was designed to evaluate the effectiveness of rivastigmine in treating the chronic neuropsychological symptoms of traumatic brain injury that contribute heavily to the degree of disability these patients display. This was a randomized, double blind, placebo-controlled crossover study of 102 volunteers. The test group underwent two periods of titration to a maximum dose of 12 mg per day, an 8-week maintenance period followed by a 4-week washout. Computerized neuropsychological testing as well as clinical interviews were employed, and rivastigmine proved significantly over placebo on testing, however there was no difference in clinical interview results. Overall results showed a positive trend toward significance.

The potential benefit of D-cycloserine in treating social impairment in autistic individuals was the subject of this paper. Measures included the CGI (clinical global impression) and the aberrant behavior checklist. In this pilot study, D-cycloserine treatment resulted in significant improvement in social withdrawal.

This study was designed to look at the effects of Modafinil, a wakefulness promoting agent on the ability of patients with first episode psychosis to discriminate emotional facial expressions. It is thought that this inability is an important component of the overall impairment in emotional functioning seen individuals affected by psychosis. In the study, forty patients with first episode psychosis were randomized in a double-blind crossover design to receive either a single dose of modafinil 200 mg or placebo. Emotional functions were measured using the emotional face recognition test, the affective go-no go task, and the reward and punishment learning task. The conclusion of the study was that modafinil did improve analysis of facial recognition in patients with first episode psychosis.


This source material is found on the NIH/National Institute on Drug Abuse web site. It contains factual information on ADHD and its treatment with psychostimulant medications. Information on the misuse and abuse of psychostimulants can be found here. The intended audience is the lay public, but it contains useful information for clinicians as well.


The stimulant medication, modafinil has been shown previously to induce overconfidence in sleep deprived subjects with regard to their state of alertness and ability to sustain attention. This study purported to investigate this phenomenon using a group of 18 healthy non sleep -deprived adults. The design was a double-blind, placebo-controlled fully within subjects manipulation of placebo and modafinil. An average of 300 mg of modafinil was given prior to three 50 min. cognitive testing sessions. The battery included subjective self-assessments of mood, fatigue, affect, vigor, and motivation, as well as cognitive assessments of reaction time, logical reasoning, visual comparison, mental addition, and vigilance. The results showed significant positive effects for the modafinil treated group with the improvement of fatigue levels, motivation, reaction time, and vigilance. The modafinil group did show a non-significant trend toward overconfidence.


This article examines the ethical issues raised by the burgeoning advances and growth of knowledge in the field of cognitive neuroscience. Both practical and philosophical questions are considered, especially in the light of applications of new neurotechnology in the life of the individual. How do these new innovations affect the way persons consider themselves as social, biological, and spiritual beings?
10. Findling R ed. Clinical manual of child and adolescent psychopharmacology Am Psychiatric publishing Inc 2008. This is a concise guide of pediatric psychopharmacology which reviews the commonly seen diagnostic entities in child and adolescent psychiatric practice, and the evidence based medication based strategies employed in treating them. This is a practically organized manual that provides the bridge between Stahl's Essentials and the busy psychopharmacologist working with children and teens in the office.

This study involved twenty two adult subjects with DSM IV ADHD in a placebo-controlled, double-blind design in which the participants were given a single dose of atomoxetine 60 mg, and tested with stop signal, sustained attention, spatial working memory, and set shifting. Compared with health volunteers, the adults with ADHD showed deficits in response inhibition and working memory. Atomoxetine treatment in the ADHD group was associated with improved performance with shorter stop signal times and lower numbers of commission errors on the sustained attention task.

The purpose of this study was to investigate the effects of the alpha 2 agonist, guanfacine on the performance of healthy male volunteers on a battery of neuropsychological tasks measuring executive functioning and memory. The sixty subjects were randomized into three groups, and cognitive testing was performed 2 and 4 hours after the double blind administration of guanfacine 1 mg, 2 mg, or placebo. Guanfacine did not outperform placebo at either dosage strength on measures of prefrontal memory or executive functioning. There was a negative effect on systolic blood pressure, and mild sedation in the guanfacine groups. This study helps demonstrate the idea that cognitively health persons may not realize the benefit of taking PCE’s that they seek, and may actually be subject to harmful side effects.

The aim of this study was to investigate potential cognitive enhancing effects of modafinil on the neuropsychological functioning of sixty healthy volunteers. A randomized double blind between subjects design was used with the conclusion that modafinil improves performance by reducing impulsive decision-making on several executive functioning and working memory related tasks.