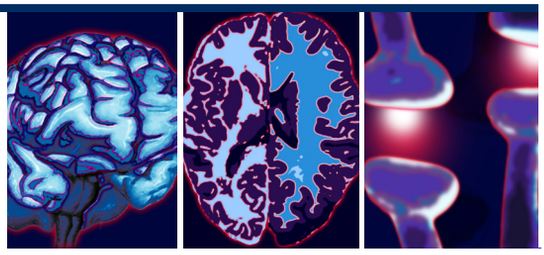

Current controversies in ADHD: diagnosis, treatment and comorbid substance abuse

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Q What originally led to your interest in attention-deficit hyperactivity disorder?

A number of disorders originate early in life and have a lifelong course associated with them. As such, attention-deficit hyperactivity disorder (ADHD) was really a compelling disorder; it starts early and in some cases seems to get better while in other cases it does not, and continues into adulthood. I was interested in ADHD because it is one of the disorders that affects cognition, and has effects on human behavior and emotion – it is a disorder that really affects all aspects of a person's life. I was also fortunate enough to work with a very senior person with an interest in the field. The final factor was that very early in my education as a resident treating ADHD, I was struck by the extent to which patients improved when

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you were able to really nail the diagnosis down and treat them. The patient can show a remarkable improvement, and it is very satisfying to see that reversal of symptoms, the improvement in functionality and the person's spirit returns.

Q Which researchers have influenced or inspired your research?

"A lot of people (other physicians and practitioners who work in this area) are skeptical of the diagnosis of ADHD, primarily because it is such a retrospective diagnosis."

I started working with Dr Joseph Biederman (Massachusetts General Hospital, MA, USA), a very prominent researcher and clinician in this area for many years, and I continue to work with him. He mentored me for a number of years and now we are colleagues; he was very influential in my interest in ADHD and related disorders.

Other than Dr Biederman, there were a number of researchers that I think produced work that was very important in terms of the interests I had. For example, one of the people who has written in this area for many years is Russell Barkley (State University of New York Upstate Medical University, NY, USA), who conducted research aiming to provide a conceptual understanding of what ADHD is and where it comes from. Another person is Keith Conners (Duke Medical Center, NC, USA). I have an affection for some of the treatment issues surrounding ADHD (e.g., pharmacotherapy) and Dr Conners has always had elaborate methodology and outcome measures for assessment – showing really innovative thinking very early on surrounding the treatments for ADHD. I have been interested in his treatment work. Dr Paul Wender (formerly of University of Utah, UT, USA) has also influenced my work, owing to his interest in adult ADHD. He was very interested in adult ADHD and conducted trials before it was fashionable and before people realized ADHD in adults was an issue. Paul Wender was, in many ways, the father of adult ADHD and conducted seminal, innovative research in this arena. Finally, there is Professor Jan Loney (University of Iowa Children's Hospital, IA, USA), who carried out longitudinal studies on ADHD and touched on substance abuse, which is one of the areas I specialize in. I have found some of her research to be very innovative and helpful.

Q What has been your biggest achievement in the field?

In ADHD there are two areas that I have really focused on. One is the overlap between ADHD and substance abuse. I am also an addictionologist in addition to adult psychiatry and child and adolescent psychiatry, and have been interested in merging those fields to examine the developmental relationships between ADHD and substance abuse. While I cannot say I conducted the first project in this area by any means, I have been involved in systematically and comprehensively looking at this area to tie together discordant research. I have examined the research from all aspects, looking at the developmental relationship, the prevention of substance abuse in ADHD, looking at treatment issues associated with it and identification of substance abuse in ADHD and *vice versa*. The work from our group has formed some of the fundamentals in this area, but I also feel that we were a catalyst. We were very fortunate that other people were interested in this area, with some groups conducting research and other individuals more clinically interested. In many ways it was about being in the right place at the right time; we were fortunate that there was, and continues to be, substantial interest in this subject and a lot of excitement and enthusiasm. I still review a number of papers and there are several recent meta-analyses confirming our work showing that ADHD is a major risk factor for substance abuse.

The other area I have worked on is investigating treatments for ADHD. Our group were among the first to discuss cognitive behavioral therapies for ADHD and over a decade ago published one of the first papers on this subject [1,2]. Subsequently, there have been a number of controlled trials funded by the NIH – two of which were published within the past year [3,4]. Another of my real interests is in pharmacotherapy of ADHD. I am interested in the unique ways of using stimulant medications, different preparations of stimulants and the longer term chronic effects of treatment. We know these medicines work in the short term, but what are the chronic effects? Do they continue to

work? What are the adverse events over time – over 2, 3 and 5 years? I am also very interested and have been active in the study of nonstimulants. We have just published a paper representing two large pediatric studies that demonstrated a negative result when using nicotinic agents for ADHD [5]. I am still optimistic that classes of nicotine-like compounds may be helpful for ADHD or related executive function problems. In those individuals that we tested, the first level studies were positive but the second level studies were negative. We recently presented a large data set of children receiving α-agonists and stimulants, and found that if you add these α-agonists to their treatment they experience a better outcome for ADHD in multiple domains, and the treatment works throughout the day. So by combining medications we are trying to help those with residual symptoms of ADHD improve executive function problems (e.g., organization, prioritization and hierarchical thinking difficulties), and are really trying to treat children and adults with ADHD so that they are not just symptomatically better but they are also well.

Q You recently conducted a study on early-morning treatment for ADHD in children. Can you describe the results & their clinical implications?

There has been some recent interest in looking at children functioning with ADHD not only during the school day, which we all know is very important, and after school, but also looking before school. To conduct the study we had to devise a scale – a before-school functioning scale – which has now been used in a number of trials because it is a more descriptive evaluation of how a child is functioning in the morning. This was a study where a different formulation of the stimulant methylphenidate was used. A patch form called the methylphenidate transdermal system was used, which is a unique way of delivering methylphenidate. This study was devised to examine early-morning symptoms and functioning in school-aged youths. The advantage of the patch in this setting was that the patch could be put on the children while they were still sleeping and therefore they did not have to be woken up to take their oral medication. We were particularly interested in what was occurring before school. For example, there were some data that indicated that if a child gets off to a bad start in the morning, it is going to be reflected later during the school day. In this study we were really focusing on the morning functioning of these children and two different sizes of patch were studied. The patch was found to work within approximately 1 h. The children were eating breakfast (one of our concerns) and we saw a dramatic improvement in many different aspects, including both symptoms of ADHD and functional proxies of symptoms of ADHD (e.g., organizing yourself, hygiene, the time it takes one to get to the breakfast table, the time it takes to get out of the house and the ability to pack a backpack). This covered many morning activities that cause great grief for the children and the families.

Q In a 2009 article, you reported the presenting symptoms of ADHD in adulthood [6]. What difficulties are experienced when diagnosing adults with ADHD?

There are a number of diagnostic issues regarding ADHD in adults that have become problematic. One problem is that people present who are 40 years old who are then asked to remember if they had symptoms of this disorder before the age of 7 years and are unable to do so. Most people can remember the track of symptoms particularly through college, young adulthood and into their current adult status, but it is often a difficult issue for people to be able to anchor diagnostically prior to 7 years of age. Our group is facing the challenge of trying to compare people with current symptoms of ADHD who cannot remember the onset of their symptoms with more of a prototypical adult with ADHD. A lot of people (other physicians and practitioners who work in this area) are skeptical of the diagnosis of ADHD, primarily because it is such a retrospective diagnosis. It is also possible that some of the skepticism surrounding the diagnosis is the concern that these adults' sole purpose is to try and acquire stimulant

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medications, controlled substances, to treat their ADHD. This issue becomes mixed with the problem of treatment and people's skepticism surrounding the diagnosis.

The paper you are referring to was in many ways a replication of an earlier paper by one of our graduate students that helped us better understand the symptoms that adults most commonly present with [7]. That paper found – not dissimilar from what other papers and the literature would show – that adults with ADHD have predominant inattentive cluster of symptoms. Inattention and distractibility are still the most problematic symptoms that are being reported by the patients to their practitioners, relative to the hyperactivity–impulsivity, and this is consistent with a number of papers that have looked at children with ADHD longitudinally over time, shedding some of the hyperactivity and impulsivity and tending to retain the inattentive and distraction cluster of symptoms. This does support that, in fact, adults with ADHD have a preponderance of inattention, distraction and symptoms in those realms. However, the article also points out that adults with ADHD who primarily have inattention and distraction as their presenting symptoms, also have some hyperactive–impulsive symptoms. For example, the average adult who has the 'inattentive subtype of ADHD' also has three or more symptoms of hyperactivity–impulsivity. Therefore patients are not devoid of these symptoms, they just do not have many of them. In fact, it is a different argument or different question: what are the meanings of the different subtypes, particularly in adults? And it is not really clear whether these subtypes of ADHD are going to remain through the new diagnostic classification system that is currently underway. Our sense is that the more symptoms of ADHD the greater the severity and if you have the inattentive or the hyperactive–impulsive subtypes of ADHD, you tend to have a slightly less severe form than if you have the combined subtype, which basically means the patient exhibits enough symptoms in the two different categories to be diagnosed with the combined subtype. More symptoms typically mean more problems with the disorder, which is a reflection of a more severe form of ADHD.

"Better understanding is needed of the different underlying neurobiological subtypes of ADHD, so that it is not necessary to use trial and error medication strategies or cognitive behavioral therapy."

Q More recently you studied the effects of a neuronal nicotinic receptor partial agonist in treating pediatric ADHD [8]. How do your results compare with those of previous studies on this class of agonist in adults?

There is compelling literature that has demonstrated that nicotine and some nicotine-related compounds seem to improve ADHD and improve areas outside of ADHD-associated problems. In particular, there was quite a bit of interest in some different compounds, termed partial agonists, which are not just similar to nicotine but have components of nicotine. These compounds do not seem to be addictive and they have different effects on the cardiovascular system. Researchers were very interested in them because they seemed to stimulate the different receptors that are related to improvement in cognition, which was thought to be problematic in ADHD. Preliminary studies with these partial agonists found improvements in components of ADHD [9]. It was certainly exciting to then launch forward with a more systematic and thorough examination. The second level of intrigue particularly related to the compound ABT-089, which is a partial nicotonic agonist. Despite some of the initial adult findings being positive, the two large pediatric studies [5] were solidly negative and did not show a significant signal for ADHD. So was that disappointing? Yes. Would I say that there is no role for nicotine/nicotinic class agents in ADHD? No, because these agents have a long history in improving ADHD symptoms and executive function; however, there is going to have to be further adaptations of the molecules. A further issue that arises is related to methodology; many of the symptoms used to define ADHD have grown through the years, in part, related to response to stimulants. Therefore, some of the outcome measures used are very stimulant friendly and non-stimulant unfriendly. Stimulant medicines have been available for over 60 years and are very effective for the treatment of ADHD. In some ways you are defining what the response is, and if you are using agents that are not stimulants, they may improve people with ADHD but the response observed may not be as robust in the symptoms that are being measured. For example, it may be

that there are other areas of improvement that are not being measured but in which patients are qualitatively reporting improvement. We have seen that with nonstimulants in particular. Sometimes some improvement in ADHD will be shown – typically for stimulants – but there will be improvement in other types of symptom clusters that may not be directly queried. Again, this is more of a methodologic issue, but it is important to consider when discussing the use of nonstimulant outcomes in ADHD. Are outcomes that are based historically really the most appropriate outcome measures in this instance?

Q How do you think the understanding of these agonists will need to develop before their full potential can be realized?

It will be important to try and understand what specific types of subunit, and what affinities, are necessary to elicit procognitive effects, what exactly the procognitive effect is in people with and without ADHD and how these effects can be measured most effectively. This concerns a number of different subunits, largely nicotinic subunits, of which there are three in particular that appear to be most important for the procognitive effects of these agents. It will be necessary to harness them more effectively and have a better preclinical understanding so that the most effective agent can be used moving forward. At the same time we have to understand the side effects that these different full or partial agonists have at the nicotinic receptor. The intention is to replicate some of the procognitive effects nicotine is known to have, but it is important to be mindful of the long-term adverse effects of nicotine that will need to be avoided.

Q How does treatment of adult & pediatric ADHD differ?

In large part there is a lot of similarity between treatments across ages, and in fact it is reasonable to test new compounds in adults prior to children because there is a similar response across the lifespan with some caveats. With regard to the ethical component, adults can give consent and assent for their own treatment as opposed to children who have a parent consenting for them. Quite honestly, if you have adverse events, particularly serious ones, it is preferable that they are in adults as opposed to children, as they will have consented more ethically to the treatment.

In addition, adults are able to report if there is any improvement in a signal, even if that signal is not being evaluated directly – adults can self-reflect on things and can give self-reports that are better than those of a child. Children's self-reports are particularly unreliable and not particularly valid, whereas an adult's self-report is very reliable and very valid.

Furthermore, when treating children with new compounds, there is always the concern that some kind of deleterious developmental effect will occur that you may not know about; whereas with adults it is possible to get some sense of this if they are on the medication for a period of time.

Having said that, the one caveat is that, for whatever reason, it seems that medicines may work a bit better in children than in adults. This may be because children have more symptoms or may be because children are being observed by parents, teachers or other caregivers and thus have multiple observers, or it may just be the underlying neurobiology – perhaps children's ADHD is more responsive to medication. There have been some medicines in development where the trials in adults were negative but those in children were positive. This is very interesting and could be because the medicine was not dosed high enough in adults or some other undetermined reason. So there is a response across the lifespan, but it would appear that children are slightly more sensitive to the medications compared with adults. This can also be observed with compounds such as nonstimulants that have been tested through the age span; children seem to have slightly higher effect sizes and response rates but experience more side effects than adolescents and adults.

Q What research is currently being conducted in the field of ADHD & substance use disorder?

There are a number of different areas being examined. Prevalence rates worldwide are being examined. A European organization based in The Netherlands (Trimbos),

"From a treatment standpoint ... treatments are also needed for children and adults who display executive function problems in addition to ADHD ... This element is still extraordinarily impairing in a number of ADHD sufferers' lives..."

is looking at ADHD and substance abuse. There is a lot of interest in the question of what happens if you overlap the neurobiology. Both ADHD and substance abuse affect dopamine, although one more in the mesolimbic system and one in the mesocortical system – but what is the overlap? It cannot be coincidence that bidirectional overlap occurs and it cannot be a coincidence that some of the treatments used for ADHD are substances of abuse in other fields (stimulant medications). So, work is being carried out to try to understand the overlapping neurobiology and why some people with ADHD develop substance abuse while others do not. There is also interest in the prevention component – another area our group has been very involved in. Treating ADHD reduces smoking and substance abuse and while that effect is very strong in adolescents, it begins to be lost in adulthood. Is this because people stop taking their medicines or is it that the age of risk is not fully appreciated in adolescents? This is an area where better understanding is needed. Finally, it is important to look at what needs to be done for current addicts who have ADHD. There has been a series of studies that have looked at treating those with active addiction and ADHD. The studies show there may be some improvement in ADHD and some nominal improvement in substance abuse [10,11]. So might it be necessary to have brief abstinence before starting medications for ADHD? We carried out a study on this and found significant improvements in people who were briefly abstinent from alcohol. Improvements were seen in alcohol consumption and ADHD but there were still issues with drinking. So, there is still a lot to be done to find the appropriate treatment – should we be using structured behavioral cognitive therapies and if we use medicines, when should we be using them?

"There also needs to be more emphasis on prevention, from an educational or interventional standpoint. For example, what help can you give the parents of an 11-year-old child with ADHD so that their child does not smoke cigarettes or become a substance abuser? There is much research to be done."

Q What clinical research is required in the field of ADHD over the next 5–10 years?

There is a tremendous amount of research directed at understanding the neurocircuitry and how it overlaps with genetics, for example, rare variants (people with specific mutations). Better understanding is needed of the different underlying neurobiological subtypes of ADHD, so that it is not necessary to use trial and error medication strategies or cognitive behavioral therapy. The solid diagnostic underpinnings need to be understood. For example, there has been considerable interest in Europe in using electroencephalograms and evoked brain potentials to look at brain functioning in ADHD and whether this can be used diagnostically. From a treatment standpoint, better pharmacologic and nonpharmacologic treatments are still needed for ADHD, and treatments are also needed for children and adults who display executive function problems in addition to ADHD, which present almost another cognitive comorbidity. This element is still extraordinarily impairing in a number of ADHD sufferers' lives. Another area is the need to better understand how to treat ADHD comorbidities, for example, mood dysregulation, depression or anxiety, and sleep disorders.

In terms of substance abuse, one of the biggest questions is: how can we prevent it and should it be treated? If we can begin to understand the neurobiological overlap between ADHD and substance abuse then we can start to have a better understanding of predictors for who is going to experience these problems. There also needs to be more emphasis on prevention, from an educational or interventional standpoint. For example, what help can you give the parents of an 11-year-old child with ADHD so that their child does not smoke cigarettes or become a substance abuser? There is much research to be done.

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