Pharmacological Test Confirming the Diagnosis: Responding to Stimulants Neuropsychiatric ADHD

Klaus Martin Beckmann
School of Medicine, Griffith University, Logan Campus, Queensland QLD 4131, Australia
*Corresponding Author: martinbeckmannnn@hotmail.com

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Abstract ADHD is a neurodevelopmental life time high prevalence disorder. Many individuals who suffer from ADHD benefit from treatment. For a significant subgroup of patients with the diagnosis ADHD, medication is important for treatment. Diagnostic criteria however as yet are not pathognomonic. A specific test to diagnose the type of ADHD that responds to medication has so far not been promoted as such. This article postulates that many individuals presenting with ADHD syndrome are likely to benefit from such a test. Here such a test is described.

Keywords ADHD Diagnosis, Diagnostic Test, ADHD Medication, Specificity, Sensitivity

1. Introduction
ADHD (attention deficit hyperactivity disorder) is a medical condition that leaves the suffering individual impaired in more than one area of life [1]. ADHD has been identified as a disorder many decades ago. [2] It is one of the most researched psychiatric conditions [3]. It is a treatable condition [4]. This paper contributes by building on previous work in the field, but interpreting findings in a new way: there is ample evidence that patients benefit from stimulant medication [5]. However this does not apply to all patients with ADHD [6]. This suggests that there is a type of ADHD that responds to stimulant medication - and a type of ADHD that does not respond to stimulant medication [7]. This paper emphasizes this fact. A trial of stimulant medication can be used in a clinical context to identify those patients who respond to medication. A success of such a response can then be seen in the 3 core domains: activity level, impulsivity and attention. This paper separates ADHD syndrome as a broader diagnostic entity (syndrome) from the specific neuropsychiatric ADHD (disorder), the type of ADHD that responds to stimulant medication. This paper then promotes a trial of ADHD stimulant medication as a diagnostic test, highlighting benefits, side effects and limitations.

2. ADHD Syndrome
Syndrome in medicine and psychiatry is a collection of signs and/or symptoms that can typically be found in a single condition. In many syndromes [8] an underlying genetic cause can be identified. In ADHD the specific genetic cause has so far not been identified. Candidate genes however have been identified [9]. Major classifications ICD – 10 [10] and DSM -5 [11] detail the collection of symptoms. ADHD is a controversial concept lacking specificity [12].

3. Neuropsychiatric ADHD
ADHD is an umbrella term including a multitude of conditions. Individuals who suffer with ADHD present with ADHD syndrome as mentioned in the previous paragraph. This is notwithstanding that a significant number [3] of patients presenting with ADHD do have the underlying neuropsychiatric condition ADHD that responds to ADHD medication [13]. This article acknowledges the differential diagnostic issues. However for the purpose of the ADHD test as outlined below, this article focuses on neuropsychiatric ADHD that responds to medication only.

4. ADHD: Stimulant Medication Diagnostic Test
Several medications are licensed for treatment if ADHD. Foremost there is the group of stimulants: methylphenidate, dexamphetamine, and also L-amphetamine and modafinil. These four stimulants exercise their effect by dopamine reuptake inhibition and direct release. L-amphetamine has noradrenalin agonistic effects too. [Other groups of medication are not referred to here as these are not relevant for the purpose of this paper. These are the medications that work through noradrenalin reuptake inhibition and a2-adrenergic agonism. These medications [14] do not have
the immediate and direct onset of effect on the triad of ADHD symptoms: overactivity, distractibility and impulsivity. Beneficial effects of non stimulant medication have a time lag of several days.

Methylphenidate and dexamphetamine in particular can be used for the diagnostic test: especially these two medications act rapidly, they have a short half life of a few hours, there is a clear linear dose response relationship, side effects are predictable and if there are side effects these usually abate rapidly, generally there are safe to use and well tolerated. At maximized dose they have a very observable and convincing beneficial effect. They are both “response”, alternatively “non response” medications [15]. For details on medication regime please contact the local treating health professional. This article does not take responsibility for individual patient’s choice on medication and or dosing regimen.

Side effects of stimulants commonly include, during the time the medication exercises its effect, i.e. during the diagnostic test: appetite suppression, sleep difficulties, abdominal pain. Less commonly can be seen, during the time the stimulant has its effect on ADHD: a worsening of tics, irritability, tearfulness, anxiety, headache, increase in blood pressure, rapid heartbeat, skin picking and nail biting and skin rashes. Behavioral rebound of ADHD symptoms can sometimes be observed when medication effects wear off. Very rarely over focus, hallucinations disordered thinking and blood dyscrasia like neutropenia may occur [16] during the time the medication exercises its effect, i.e. during the diagnostic test. Rare events have been raised in the past: historically there were concerns regarding cardiac safety, but these concerns appear to have been overemphasised [16]. To appraise the evidence for cardiac safety the following studies are referred to: one study reports an estimated annual sudden death rate with stimulants at 0.25 per 100 000 [17]. However the background rate of annual sudden death in the comparable general population has been reported higher at between 0.6 and 6 sudden cardiac deaths per year per 100 000 [18]. A large retrospective study looked at 42612 person-years of stimulant use. These researchers had access to 10 years of health insurance data which they linked in with death registry information. This study found no cardiac deaths in those 42612 person-years [19]. Importantly these authors found a background rate of 4 per 100 000 sudden cardiac deaths per year in the comparable population. These days American Pediatric Association and American Heart Association guidance [20], NICE guidance [21] advise to consider an electrocardiogram in those clients with a history of palpitations, irregular heart beat and or a family history of significant cardiac disease. Stimulants do not trigger or worsen epileptic seizures; electroencephalogram is not indicated prior to a trial of stimulant medication [22].

Table on side effects of stimulants:

<table>
<thead>
<tr>
<th>Commonly occurring side effects during the time the medication exercises its effect, i.e. during the diagnostic test:</th>
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<td>• appetite suppression</td>
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<td>• sleep difficulties</td>
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<th>Less commonly occurring side effects during the time the medication exercises its effect, i.e. during the diagnostic test:</th>
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<td>• worsening of tics</td>
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<td>• irritability</td>
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<td>• tearfulness</td>
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<td>• anxiety</td>
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<td>• skin picking</td>
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<td>• nail biting</td>
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<td>• skin rashes</td>
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Very rarely occurring side effects during the time the medication exercises its effect, i.e. during the diagnostic test:

• over focus
• hallucinations
• disordered thinking
• blood dyscrasia like neutropenia

Pharmacodynamics influences duration of medication effects. Methylphenidate, for example is broken down mostly by the enzyme carboxylesterase-1 [23]. This enzyme is known to have numerous polymorphisms. This means that some patients will metabolise Methylphenidate more slowly than individuals with another carboxylesterase-1 variant. The prevalence of these polymorphisms varies depending ethnicity, i.e. whether of Asian, of Black or of White ethnicity. This may explain why some individuals have a differently maintained response than others and why some individuals have more side effects than others.

Table on the test:

A beneficial clinical response in the 3 domains of attention, distractibility and activity levels can be observed 30 – 60 minutes following indigestion of a short acting stimulant. This test gives indication whether there is a neuropsychiatric type of ADHD which responds to stimulant medication or not.

5. Conclusions

ADHD is a highly prevalent condition. There is an ADHD syndrome and there is also a neuropsychiatric type of ADHD which responds to stimulant medication. Differential diagnosis between the two conditions cannot always be clarified clinically. These two conditions can look similar at clinical assessments. A specific and sensitive test is a trial of a short acting stimulant medication. This generally is a safe pharmacological test. If indicated cardiac status needs to be confirmed as normal. Once it is confirmed there is no relevant cardiac abnormality it is safe to proceed with stimulant medication trial. A good clinical response in the 3
domains of attention, distractibility and activity levels, which can be observed after 30 - 60 minutes following indigestion, gives indication whether there is a neuropsychiatric type of ADHD which responds to stimulant medication or not. The advantage of such a test is that those with no neuropsychiatric type of ADHD which responds to stimulant medication will not be unduly exposed to ADHD medication after the negative trial. Limitations to such a trial are that some individuals may need a higher dose to clarify response or non response. A once off trial will not be sufficiently sensitive. A possible solution to this non response may be to trial an adjusted dose. A further and significant limitation of this article is that no direct instructions are provided how stimulant medications can be titrated. The reason for this limitation is the author wishes to eliminate any possibility for medication error. The reader is advised to seek a competent health professional for diagnostic clarification and safe management of any treatment - whether psychosocial with medication (or without medication). A critique may be that such a test measures what it purports to measure, a tautology. Such a pleonasm can be refuted as this paper has direct applicability to clinical practice. Immediate response to stimulant medications is quoted as between 50 % and 90 %. In other words this means that 50% to 10% of patients where medication is being considered as treatment for ADHD will immediately learn that stimulant medications are not as beneficial as hoped. Such an event may occur for reason that there is no underlying neuropsychiatric type of ADHD which responds to stimulant medication. Such ADHD symptoms may then need to be explained differently than neuropsychiatric type of ADHD which responds to stimulant medication. This stimulant medication tests assists with excluding or confirming a formal diagnosis. This test has high sensitivity and specificity.

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REFERENCES


