Journal of
Pharmacology & Clinical Research
ISSN: 2473-5574

Juniper Publishers
key to the Researchers

Mini Review
Volume 3 Issue 3 – July 2017
DOI: 10.19080/JPCR.2017.03.555614

J of Pharmacol & Clin Res
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Towards A Personalized Medicine Approach for the Titration of Pharmacologic Treatments in Children with ADHD

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Submission: July 13, 2016; **Published:** July 21, 2017

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Diagnosis of ADHD

The most commonly used criteria for the diagnosis of attention deficit and hyperactivity disorder (ADHD) hyperkinetic disorder are those provided in DSM-V-TR and in ICD-10. These definitions are based exclusively on clinical evidence on maladaptive high levels of impulsivity, hyperactivity and inattention. They are all based on observations about how children behave, but all are shown by individual children to different extents, and are influenced by context as well as by the constitution of the person. The differences in the definitions between DSM-V and ICD-10 historically has their origin in diverging practice between North America and Europe: in North America moderate to severe levels were recognized and termed 'attention deficit hyperactivity disorder'; in most of Europe, only extreme levels were seen as an illness and called 'hyperkinetic disorder'.

ADHD (as defined in DSM-V) is a common disorder, whereas the more restricted diagnosis of hyperkinetic disorder in ICD-10, representing a severe sub-group of DSM-V combined type ADHD, is naturally less common. From this historically diverging perspective, the terminology in Europe has changed, and 'ADHD' has become the diagnostic phrase most commonly used in practice, even when more restrictive criteria are being used.

More recent extensive biological investigations of both ADHD and hyperkinetic disorder have yielded some neuro imaging, quantitative EEG and molecular genetics associations; neuro cognitive theories have emerged [1-3] and there is a better understanding of the natural history and the risks that hyperactive behavior imposes [4]. Nevertheless, the disorder remains one that is defined at a behavioral level, and its presence does not imply a neurological disease. Despite these findings, and like all psychiatric disorders, ADHD is diagnosed only based on the presence of particular behavioral symptoms that are judged to cause significant impairment in an individual's functioning, and not on the results of a specific test. In fact, recently pub¬lished ADHD evaluation guidelines from the American Academy of Pediatrics (AAP) explicitly state that no particular diagnostic test should be routinely used when evaluating a child for ADHD.

The Use Of Quantitative EEG As Diagnostic Tools

The fact that biologic, neuroimaging, quantitative EEG (qEEG) and molecular genetics findings are currently not included in the diagnosis of ADHD as described in DSM-V or IDC-10 partially explains the difficulties of diagnosis as a practical accomplishment due to the language and specificity of the criteria and the need of accurate differentiation from coexisting conditions. At this purpose, qEEG might be a helpful diagnostic tool. The use of qEEG is based on findings that individuals with ADHD have a distinctive pattern of electrical brain activity that is often referred to as "cortical slowing". This type of electrical brain activity is characterized by an elevation of low frequency theta and delta waves (which is associated with feeling drowsy) and a reduction of higher frequency beta waves (which is associated with 'alertness' and intentional and memory processes)in the prefrontal cortex. Theta wave activity is associated with an unfocused and inattentive state while beta activity is associated with more focused attention. Thus, an elevated theta/beta ratio reflects a less alert and more unfocused state.

In past studies, roughly 90% of individuals diagnosed with ADHD based on a comprehensive evaluation tested positive for this EEG marker. In contrast, about 95% of normal controls tested negative. Thus, while not a perfectly reliable indicator, the sensitivity and specificity of qEEG in identifying ADHD was extremely strong [5] if compared to normal controls. Recently, in children with ADHD of the DSM-IV combined type (ADHD-C) higher theta and alpha activity was found with the most prominent effect in the upper-theta/lower-alpha (5.5–10.5

Hz) range [6]. In children of the predominantly inattentive type (ADHD-I), a significantly higher theta/beta ratio was observed at single electrodes (F3, Fz) and a tendency for a higher theta/beta ratio when considering all electrodes (large effect size)

Pharmacologic Treatments for ADHD

Currently, atomoxetine, guanfacine extended release, dexamfetamine and methylphenidate are confirmed to be effective medications in controlling the symptoms of ADHD in children and young people with respect to no treatment. Both, psycho stimulants and non-stimulants (atomoxetine or guanafacine extended release) acts within the brain by increasing the extracellular availability of dopamine and noradrenaline at the synaptic cleft. The alteration in the availability of these relevant neurotransmitters changes the excitability of the group of neurons. Thus, quantitative EEG (qEEG) might useful not only as a diagnostic aide for ADHD, but also for the establishment of the treatment effect of an administered medication. Therapy with any of the three ADHS medications (atomoxetine, dexamfetamine or methylphenidate) is usually initiated by gradually increasing the dose to minimize typically side effects. Though some individuals are sensitive to lower doses, there is no detailed guidance on how treatment effect should be established other than with clinical observations on the individual's behavior. Also, the dosing neither foresees any individual weight adaptation nor it considers metabolic changes of a individual growing of the treated subject. In addition to this, clinical parameters require longer observation periods, might be more negatively affected by subjective biases and might be less sensitive than a quantitative measurement of treatment effectiveness.

As a consequence, there is an unmet medical need for a non-invasive quantitative assessment tool, which allows, adapting individually the treatment dose for medication active on the CNS, to monitor the effectiveness of the treatment over time easily, and to allow a flexible modification of the personalized treatment, when needed. Such an approach would be extremely beneficial in subjects with ADHS, since the treatment might start at relatively early age, in individuals with a brain under development, in which the pharmacological impact should be hold at the minimum doses needed. The finding of the individual minimum effective dose might even more relevant when a psychostimulant drug has been chosen for the treatment of ADHS.

Neuro Feedback As Treatments Alternative For ADHD

Quantitative EEG technology is also used in an alternatively treatment approach, based on the concept of biofeedback. Electroencephalography (EEG) biofeedback (so-called neuro feedback) has been developed as a non-invasive non-pharmacologic treatment for children with ADHD since 1970s, and is also after the licensing of pharmacologic treatments still widely used. Its rationale lies in theories of brain plasticity and cortical self-regulation that suggest it may be possible to countermand deficits of cortical activation. The use of neuro feedback derived from the initial hypothesis of Satterfield and colleagues [7,8] that attentioal deficits result from dysfunction of the central nervous system and that children with ADHD exhibit behaviors consistent with 'under arousal'. It is assumed that variations in alertness and behavioral control are directly related to specific thalamocortical generator mechanisms and those variations are evident in distinctive EEG frequency rhythms that emerge over specific topographic regions of the brain [9]. It is proposed that ADHD neuropathology could alter these rhythms and that EEG biofeedback training directed at normalizing these rhythms might therefore yield sustained clinical benefits. These observations on the switch of EEG rhythms might be useful as hallmark to establish an individual treatment response to a pharmacologic treatment.

Assessing a Pharmacological Treatment Effect and Individual Doses through qEEG

Difficulties emerge not only at the time of diagnosis of ADHD, but also once effectiveness of treatment dose has to be established, since the clinical gold standard requires a social-behavioral grading, only.

How difficult the establishment of a full-treatment response for a given dose can be with the use of clinical parameters only, is emphasized by the observation , that the problems associated with ADHD appear in different ways at different ages, as the individual matures and as the environmental requirements for sustained self-control increase [10]. Quantified EEG assessments could represent this sensitive tool, supporting clinical decision making.

Indeed, pharmacological treatment for ADHS, which passes the blood - brain barrier, might interact with the same neurological network trained through bioelectrical neuro regulation of the biofeedback techniques. With neuro feedback, the intentional modulation of cortical self-regulation is achieved through a process of operant learning through the provision of training aimed to decrease excessive theta or slow wave (delta) activity and increase beta activity. Similarly, the pharmacological treatment for ADHD at the individually appropriate dose should show on quantitative EEG (qEEG) recordings similar effects on theta, delta and beta activities.

Proposal for a Study To Verify The above Hypothesis

By means of a pilot study in a small sample of subjects with ADHD of the DSM-IV combined type (ADHD-C)the decision making on individual minimum dose-finding through qEEG should been compared to a clinical assessment by means of a structured Video-Analysis. Forty individuals might be sufficient for such a purpose.

The sample should include children of both sexes at the ages from 5 to 12 years, with recent diagnosis of ADHD, but treatment

How to cite this article: Manolo E B. Towards A Personalized Medicine Approach for the Titration of Pharmacologic Treatments in Children with ADHD. J of Pharmacol & Clin Res. 2017; 8(3): 555614. DOI: 10.19080/JPCR.2017.03.555614.

naïve for this condition. Concomitant medications, which might pass the blood-brain barrier has to be stable for at least 1 month prior to baseline assessments for this study. In childhood, as many as 65% of children with ADHD have one or more co-morbid conditions, including oppositional defiant and conduct disorder, anxiety and mood disorders, tics or Tourette syndrome, learning disorders and pervasive developmental disorders (e.g. autism) [11-13]. These co-morbid conditions might represent an important confounding factor. If it might be possible to reduce the range of co-morbidities included in this study, it would be an advantage.

The study should foresee 4treatment groups, with 10 subjects each group:

a) Atomoxetine,

b) Guanfacine extended release,

c) Dexamfetamine,

d) Methylphenidate, and

Subjects should be assigned randomly to each of the 5 treatment options. The raters have to be blinded to the treatment received by the subjects.

Two types of assessments will be performed at each session: qEEG and clinical rating of improvement.

Quantitative EEG analysis will be based on 300 s (5 min) of artifact-free EEG recording. The EEGs will be derived from Frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrodes referenced to the contra lateral A2 or A1 electrode respectively. The low-pass filter should be set to 40 Hz, while the high-pass filter should be set to 0.5Hz. Data should be digitized with sampling rate of 128 Hz and a 0.78-μV resolution. Digitized EEG derived from C3-A2 will then be assessed by a fast Fourier transform for consecutive 2-second epochs (decimation in frequency fast Fourier transform algorithm, Sande-Tukey [14] (Oppenheim et al, 1975); Turkey window tapering [15]. The resulting spectra will be averaged over 300 s. Power spectra will be divided into spectral segments corresponding to 0.5 to 4.5, 5.0 to 7.5, 8.0 to 12.0, 12.5- to 16.0,and 16.5- to 25.0 Hz.

A Multidimensional rating scale should be used to assess multiple domains of impairment. The [16] Functional Impairment Rating Scale [16,17]. After a baseline recording of qEEG and a clinical evaluation of the clinical symptoms and signs, the subjects should receive the recommended starting dose for the given treatment group for a week. Thereafter a first session with qEEG and clinical improvement rating will be performed. Once the session has been completed, the dose will be increased to two times the starting dose for week 2. Other sessions will follow at the same time intervals, and dose increases will continue as stepwise increase of multiples of the starting dose. The recommended maximum dose will never been exceeded. Once a further dose increase is not providing any additional benefit neither in terms of qEEG findings nor for clinical aspects, the previous dose will be defined as the optimal dose. The identified optimal dose will be continued for one year. At this stage a long-term outcome session will be performed to evaluate the maintenance of the improvements achieved.

During the time period in which the subject will be treated with the optimal dose, regular assessments from parents could be collected by means of DuPaul, et al. [18] ADHD-Rating Scale.

Conclusion

The study should provide the opportunity to identify individually the optimal dose for the subject. This treatment approach would replace the concept of the minimal effective dose. The optimal treatment dose versus a minimal effective dose should allow to reduce the subjects classified as non responders, and increase treatment compliance overall, by reducing side effects of the treatment. The study should also emphasize the usefulness of the qEEG tool over the clinical assessment of improvement for the definition of the optimal treatment dose. Indeed, qEEG assessment represents a purely objective method for the identification of the individual optimal dose, whereas the clinical assessment might introduce a higher amount of subjective interpretation and classification of the behavior.

The optimal treatment dose would also reduce the negative effects on the neuropsychological development of the children. The long-term follow-up session might also allow identifying any potential need to adjust the treatment dose. Though qEEG might be also helpful for this purpose, it is not clear, when this might be required. Additional studies, or alternatively a more structured long-term follow-up study of this proposed pilot study would be needed.

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How to cite this article: Manolo E B. Towards A Personalized Medicine Approach for the Titration of Pharmacologic Treatments in Children with ADHD. J of Pharmacol & Clin Res. 2017; 8(3): 555614. DOI: 10.19080/JPCR.2017.03.555614.

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DOI: 10.19080/JPCR.2017.03.555614

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