Managing the Disruptive Behaviour Prevalence with a N_{RCT}=1 Trial Registry.

Personalized Sleep Medicine –
Position Paper for the Vienna Declaration 2019

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Abstract

The personalized sleep medicine research endeavour is inspired by the clinical observation that sleep disorders in children with neuropsychiatric/-developmental disorders, who present with disruptive behaviours, are frequently undiagnosed and consequently, not or inappropriately treated. This observation elicits further questioning and a big 'Why?'. To answer these questions, on March 21st, 2019 the Department of Neurology and Section for Artificial Intelligence and Decision Support of the Center for Medical Statistics, Informatics and Intelligent Systems (Medical University of Vienna, Vienna, Austria) are hosting a Brainstorming Meeting. At this meeting, patient advocates and members of non-governmental organizations (NGOs) will report their personal experience before their sleep disorder was diagnosed and to what degree experiences they have undergone in the diagnostic process of their children and grandchildren have changed.

Our previous research has shown that currently available categorical diagnoses of behavioural disabilities do not embrace the enormous abundance of their phenotypic expressions affecting diagnostic accuracy and precision in the evaluation of therapeutic attempts. New strategies for observational phenotyping (e. g. video technology) and the exploration of patient reported behaviours are necessary to expand the spectrum of disruptive behaviour phenotypes. The identification of clinical practice-based limitations that contribute to overlooking sleep problems will help us start a change in management. Therefore, we are most interested in listening to trans-generational narratives and understanding to what degree diagnosis and treatment concepts have transformed over the years. In modern medicine, going beyond traditional uni–directional doctor–patient relationships, patients/caregivers are now taking active roles in evaluating treatment effects and making decisions about their own care. This trend has encouraged the *precision medicine* concept that considers individual genetic variability, environment and lifestyle influences for each individual. *Personalized medicine* is the description of "… a medical model using characterisation of individuals' phenotypes and genotypes (e. g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention"

[European Council Conclusion on personalised medicine for patients (2015/C 421/03)]. One way of performing **Personalized Sleep Medicine** in clinical practice is to customize treatments via an individualized single n or n = 1 approach and allows, through randomization of treatment, patients act as their own control ($N_{RCT} = 1$). We have chosen the writing N_{RCT} in order to highlight the randomization concept (medication versus placebo or vice versa), which allows meta-analysis of comparable n = 1 studies. **Personalized Sleep Medicine** sets the stage for a novel approach to treatment and monitoring: although the n = 1 approach is good clinical practice, its application as an alternative trial methodology for personalized medicine is fairly new.

Preamble

We are a group of clinicians and researchers, who are dedicated to the recognition *and* treatment of sleep and wake disorders in children and adults with developmental, cognitive and behavioural disabilities. Our experience is that the treatment of externalizing behaviours in children/youth with neuropsychiatric/-developmental disorders has been an ongoing challenge which, over the years, has raised major concerns[1] and eventually led to experimental medication trials.[2;3] Inconsolable, drastic, and despairing clinical circumstances, as well as parental or school pressure, often lead to deviations from common prescription guidelines (e. g., off-label prescriptions at a young age).[2–4] In addition, lack of sufficient available time for clinical assessments, in many geographic areas, hinders accurate monitoring of medication effectiveness.[4;5] The absence of tools to personalize treatments and monitor individualized outcomes may additionally aggravate the need to further apply over-the-counter and prescription medications.[4;5] In this context, the modulating role of sleep on wake-behaviours is missed almost completely and sleep problems are perceived as part of the underlying condition and not as treatable entities.[6]

Therefore, we decided to step back and review factors that might contribute to the current situation together with the affected individuals, patients and patient representatives. This position paper outlines the framework of this joint discussion at its very beginning. This might be one step towards shedding new light on how we understand externalizing behaviours, their natural history, treatment and consequences.

I. What are Disruptive Behaviours & How do they present?

Disruptive behaviour disorders were first defined in DSM III via three characteristic item clusters used to diagnose attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD) – all three being part of common childhood externalizing disorders.[7] Externalizing disorders frequently co-occur; ADHD is the most common neuropsychiatric/-developmental disorder in childhood, with a parental and teacher reported prevalence of 2–18 % in school-aged children, depending on sample size, study design, ethnicity, gender, age, and socio-economic status.[8] At this point, no laboratory test reliably predicts ADHD. Children with ADHD show patterns of attention deficit and/or hyperactivity-impulsivity that interferes with functioning and are perceived as inappropriate for their developmental level. Up to 60 % of those with ADHD may have a comorbid diagnosis of ODD or CD.[9] While children with ODD have severe and persistent negative, defiant, hostile, and oppositional behaviours, children with CD violate the rights of others or societal norms through repeated aggressive, destructive behaviours. Due to the variability in comorbidities among the three diagnostic groups, the development of diagnostic rating scales has still not reached any agreement.[10;11] As the causes of the comorbidities are not well understood,[12] possible genetic/epigenetic influences may be identified with Precision Medicine. A core observation in children with externalizing or disruptive behaviours is a sensory motor dysfunction, presenting with hyperkinesia and/or hypermotor-restlessness at day and night times, hyper-arousability in reactions and hypo-arousability in thinking.[13] Recently, the Video Working Group of the International Pediatric Sleep Association introduced the H-behaviours concept, which responds to this observation and creates a framework for more in-depth phenomenology describing commonalities in behavioural patterns.[14]

Disruptive behaviours are an observation-based terminology captured and described by questionnaires. H-behaviours involve characteristics that might support deciphering externalizing behaviours and monitor supplementation- or medication-based interventions in an individualized way. This may be achieved by allowing analyzing muscle tone, tension, posture, and the balance of voluntary to involuntary movements.

II. The Prescription Epidemic & Extent of Overmedication

Status-quo. Internationally, there is increasing concern regarding the high prevalence rates of psychotropic drugs being prescribed for pediatric patients. US data investigating a total of 692,485 children showed a steady increase in the prevalence of any-class and multiclass psychotropic polypharmacy from 21.2 % and 18.8 % in 1999–2000 to 27.3 % and 24.4 % in 2009–2010, respectively.[15] The prevalence increased with older age, with highest estimates for late adolescents. In 2012, Canada had the highest prescription rates for psychostimulants and antipsychotic medications for children in a multijurisdictional comparative study.[16] A recent study in Germany examined the prevalence and risks of off-label antidepressant prescriptions in minors over time, utilizing data of about two million individuals under the age of 18.[17] Among those receiving antidepressant medication, the authors found that off-label prescription prevalence rates were 58 % (2004) and 40.9 % (2011), respectively. Pediatric off-label antipsychotic prescriptions varied between 52.3 % and 71.1 % with 52.5 % presenting with a hyperkinetic disorder. Comparisons between United Kingdom (2014) and North American (USA) practice show, that UK and European guidelines are generally more conservative in their recommendations for medication use.[18] Furthermore, in North America, in the past 10 years, off-label prescribing of antipsychotic medications has risen dramatically despite serious adverse effects and a lack of strong evidence for efficacy.[16] Off-label antipsychotic use for treating disruptive behavioural challenges may result from the lack of clear guidance by experts due to the current dearth of evidence. This may produce unintended, undesirable adverse drug reactions.[2;3] Aside from differences in medical care models and time commitment of the assessing and monitoring physicians, environmental and cultural factors are important in explaining some of these differences.

Parents of children and youth with H-behaviours face social stigmas, which are associated with the underlying condition, e. g. prenatal alcohol exposure or autism spectrum disorder.[5;19] Such a stigma might lead caregivers to seek out medications and physicians to prescribe in order to attenuate the impact of challenging and/or disruptive behaviours.[4] While over the last decade advocacy work has reduced the stigmas and the general desire for medication in children with, for instance, autism,[19] such desire seems to continue in children with prenatal alcohol exposure.[20]

In North America, children/youth with H-behaviours are at high risk for overmedication and, given the trend-setting role of North American clinical practice, this may affect prescription strategies all over the world.

The Iron Conundrum. Iron deficiency (ID) has been strongly associated with abnormal sleep and wake behaviours, particularly with intractable chronic insomnia (due to Willis Ekbom disease or restless legs syndrome) and externalizing behaviours, mainly ADHD. Iron plays an important role not only in restless legs syndrome (RLS) and periodic limb movements,[21] but also in arousal disorders, such as parasomnias.[22] Iron supplementation has been shown beneficial in the treatment of intractable insomnia, RLS[23–26] and ADHD.[27;28] Proposed mechanisms are derived from iron's central role in the brain as a co-factor in neurotransmitter synthesis, as well as in myelination and oxygen delivery.[29] Iron supplementation is not without its critics: it may be harmful as a pro-oxidative element that can have negative effects on biological systems even at moderate amounts.[30] However, it has been shown to reduce ADHD symptoms in children with or at high risk of deficiencies,[31] raising questions regarding best practice and to what degree iron is safer or more harmful than pharmacological treatments.

First, the rates of prescribed psychotropic drug use among those with disruptive behaviours are high and complicated. Secondly, iron supplementation may be an underutilized therapeutic option that needs to be investigated further. Thirdly, iron deficiency might play a foundational role in future prescription practices. However, there is a gap between clinical research and practice; furthermore, current guidelines do not bridge this gap. Personalized medicine may provide answers to all these open questions and associated conundrums.

III. Individualized or Personalized Medicine

There is a need to improve the safety and efficacy of pharmacologic treatments of challenging behaviours in children/youth with neuropsychiatric-/developmental disorders, e. g., with externalizing behaviours. Accurate measurement of behavioural-improvement is vital in assessing the effective outcome of therapeutic interventions. However, involved parties may interpret behavioural-improvement differently and given the paucity of validated assessment tools, this may be a difficult and challenging process. Moreover, disruptive behaviours themselves are extremely variable in their clinical presentation, exceeding diagnostic classifications and their change over time might be missed due to parental fatigue and burn-out.[32] Participatory research and patient-oriented communication is another trend, which helps to individualize medicine.[33;34] Indeed, patients/caregivers have inspired us to engage in the development of individualized outcome measures, e. g. utilizing personally meaningful outcomes and/or video-documented change of symptoms.

A proposal for a registry-based n=1 platform. A structured approach using a combination of standard and individualized behavioural outcome measures in an n = 1 setting may generate evidence to improve therapeutic efficiency and outcome of these patients. The main principle of n = 1 is a protocol-based observation where the individual of interest is their own control. Single n or n = 1 utilizes rigorous clinical trial methodology and exceeds the classic case report or simple observational before/after study concept. In addition to providing robust evidence in a timely fashion to inform care for an individual patient, which is the main purpose of an n of 1 trial, if many patients are enrolled in the same n of 1 trial protocol, it may be possible to use meta-analysis to generate group-level estimates of treatment effectiveness. If n of 1 trial protocols are embedded in patient registries that follow the principles of registry science (e. g., near complete case coverage, standardized measurement of outcomes), there is potential for efficient implementation of high-quality n of 1 trials. The advantages of n of 1 trials over observational before/after designs or case reports include:

1. randomization to multiple rounds of intervention/control conditions in order to control for temporal confounding;
2. the ability to launch placebo-controlled or comparative effectiveness trials with blinding of participants and outcome assessors where this is appropriate, and
3. prospective definition of standardized individual outcomes and their measurement. In common with other types of cross-over trials where individuals serve as their own controls, n of 1 trials are suitable for outcomes or trial end-points that can capture short-term and transient (reversible) changes. The creation of a registry-based online platform that includes standard protocols for n of 1 trials will enable health care providers from various countries and institutions to evaluate pharmacologic interventions in children/youth with neuropsychiatric-/developmental disorders, in order to inform individual treatment decisions while also contributing information toward a rigorous multi-centre evaluation. The results for each individual patient may be used to support care decisions for that patient without waiting for the group-level results from the larger meta-analysis across multiple centres.

IV. Motivation and Goal of this Position Paper

There is a need to improve the safety and effectiveness of pharmacologic treatments of challenging behaviours in children/youth with neuropsychiatric/-developmental disorders. An approach using individualized behavioural outcome measures in

an n = 1 setting may personalize/individualize and improve therapeutic efficiency and outcome for these patients. The first step is to develop outcome measures for disruptive behaviours and N_{RCT} = 1 protocols for test-settings.

As a first step towards our overall goal, a task force of clinicians and patient advocates have justified the research endeavour with this position paper. On March 21st, 2019, we will review and prepare together with interested patient advocates and non-governmental organizations (NGOs) the first framework for applying n = 1 study design in clinical practice. This framework will then be reviewed by professionals and lay-people members of our research consortium. This Position Paper, its review and further development, will be the basis for grant applications to further develop an n = 1 trial platform and personalize pediatric wake and sleep medicine.

Appendix

The Proposed Research. Step 1

The first step in creating a personalized n = 1 treatment protocol for children with neuropsychiatric/-developmental disorders is to develop outcome measures for interventions when disruptive behaviours are treated. An example, which even convinced insurance companies and billing services in Germany, is the methyphenidate titration study for individualized treatment interventions.[35;36] The subtle changes in facial mimic characteristics, as a main measure for self-regulation in children/youth with ADHD, were investigated utilizing video recordings. Smiling, captured collaboratively by parents and professionals, became key to medication titration on an individual level avoiding under-/ over-dosage of psychostimulants and adverse drug reactions. The focus on sleep[37;38] or specific clinical (e. g. biochemical) outcome measures[39;40] and their evaluation is another complementary approach.

Goal of Step 1. Following the need for personalized treatments and individualized outcomes, we will test applicability of available tools for n = 1 study-protocols, which allow meta-analysis-based evaluation of both quality assurance and research-based n = 1 studies. Given our engagement with pediatric patients and the need to improve clinical monitoring of pharmacologic therapies for children with challenging wake and sleep behaviours, these highly vulnerable populations are the particular focus of our research.

Hypothesis. Capturing the change of symptoms at an individualized level via tailored outcome measures (e. g., 'ADHD-smile' or increase of 'vigilance') will better respond to the patient's/families' personal medication related experience. This approach will also strengthen the unique subjective perspective regarding effect size, and consequently the satisfaction, adherence, and involvement in subsequent decision-making processes of patients thus, the creation of a participatory research network.

Objectives. In order to achieve this goal, in our research endeavour we will

1. *Integrate* traditional symptoms of externalizing behaviours ('core outcomes' defined via validated questionnaires) and personalized outcome measures (e. g., sitting behaviours at dinner table) in randomized $N_{RCT} = 1$ protocols, which can be used in evaluation of any of the following mentioned interventions in patients with disruptive or H-behaviours.
2. *Develop exemplary clinical protocols* for n = 1 trials for (a) iron supplementation and (b) interventions with short acting stimulant treatments.
3. *Develop user-friendly consent/assent* forms utilizing modern layout and graphic control elements, (e. g., use of space and icons) and tailored to specific age and patient groups, considerate of the needs of the recipient.

Expected Deliverables

Core sets of assessment tools & individualized outcome measures for the evaluation of pharmacological therapies in children/youth with disruptive behaviours, utilizing the H-behaviours concept.

1. *A library of individual H-behaviour symptoms, visualized by pictograms and/ or videos,* for parents/ caregivers with the ultimate goal to be used in parental and clinical monitoring.
2. *For achieving (1) and (2) an electronic process book and user guide will be developed. This will enable the creation of individualised patient related information,* highlighting the pictograms and or use of videos as visualized outcome measures to be of use to a wider clinical audience.

Benefits

1. **Clinical Applicability:** Aside from traditional symptom monitoring (via questionnaires), the applicability and user-friendliness of the tools offered in this research endeavour will enable personalized pharmacological treatment of children/youth with neuropsychiatric/-developmental disorders, both in practical clinical settings and in formal trial settings.
2. **Research Applicability:** Collected data will support detailed phenotyping of disruptive behaviours utilizing the H-behaviours concept from a clinical and pharmacological aspect.
3. **Applicability in quality improvement:** This project will improve information prioritization and communication with patients and improve the consenting/assenting process.

In summary, this *Position Paper,* its review and further development, will be the basis for grant applications to further develop an n = 1 trial platform and personalize pediatric wake and sleep medicine.

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