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EDITORIAL

Re-thinking treatment targets in child and adolescent psychiatry

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In 1970, Robins and Guze proposed five steps to achieve valid classification of mental disorders: clinical description, laboratory study, exclusion of other disorders, follow-up study, and family history [1]. Those steps helped establish significant validity (defined as a coherent syndrome clinicians can describe and measure) and reliability (meaning different clinicians agree on the same diagnosis) for specific psychiatric disorders, leading to consistent definitions of "natural" outcomes, specific responses to therapeutic interventions, and prognosis. Diagnoses in psychiatry are still based on clinical constructs defined by observation and patient's reports. The ways diagnoses are formulated influence the design of innovative treatments and not always for the better. Patients are usually included in clinical trials based on specific mental diagnoses and narrow enrolment standards to ensure homogeneous samples. That limits the applicability of findings in everyday practice because specific symptoms often overlap among psychiatric diagnoses, as do psychiatric and medical comorbidities, with significant impact on diagnostic formulation, prognosis and treatment choices.

Initiatives such as RDoC or ROAMER [2, 3] call for increasing clinical and biological research to develop innovative research-oriented diagnostic formulations based on dimensions of observable behaviour and associated neurobiological characteristics, rather than on specific diagnostic "categorical" entities. This approach may be particularly relevant in the case of child and adolescent psychiatry. In fact, with the significant exceptions of conditions such as attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD), in which the full clinical symptomatology usually appears in early years, the clinical description (and corresponding validity and reliability) of many mental disorders in children are adapted from the corresponding adulthood clinical presentations. Yet, in children and adolescents, the age-specific clinical presentations for these disorders frequently include a combination of non-specific symptoms, leading to delays of diagnosis and treatment implementation, which in turn may increase clinical impairment and reduce patient wellness.

Highly impairing clinical presentations such as severe irritability and emotional lability frequently appear as unspecific symptoms of different developmental psychiatric disorders such as ADHD, oppositional defiant disorder (ODD), conduct disorder (CD)/disruptive behaviour disorder (DBD), intermittent explosive disorder (IED), disruptive mood dysregulation disorder (DMDD), or anxiety disorder (AD) and often also ASD. In fact, severe irritability is one of the most common reasons for referral to child and adolescent mental health services [4], and is associated with significant functional impairments and exceptionally poor long-term outcomes [5] as well as increased suicidality [6]. Those associations are independent of the specific categorical diagnosis, and there is a significant gap between their impact on clinical burden and the available therapies we can offer to our patients. The article by Wesselhoeft et al. [7] in this issue, using data from 3435 children aged 7–10 years from the Danish National Birth Cohort, provides evidence to support the importance of severe irritability in mental health. The authors studied dimensions and subtypes of oppositionality, and find that, among the dimensions emerging from a three-factor model (angry/irritable, argumentative behaviour, and vindictiveness), the angry/irritable dimension was associated with high emotional problems and disorders and fewer social skills or positive attributes. Among the four oppositional defiant disorders identified, those with a predominance of angry/irritable symptoms were characterized by comorbid

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psychopathology, increased functional impairment and psychosocial problems. The study suggests that irritability is a clinical characteristic modulating presentation and prognosis and, therefore, a potential treatment target.

Irritability has been defined as an increased predisposition to anger compared with peers at the same developmental level including both behavioural and mood dysregulation components [8]. Irritability rises during normal early childhood development, peaking in preschool years, and declines thereafter, with another increase in adolescence. Self-regulation of irritable mood and behaviour occurs thanks to the development of cortical structures mediating emotion regulation and early executive function capability [9]. Emotion regulation plays a central role for the modulation of irritability, although there are few studies of the normative use of emotion regulation strategies over age. The few available data suggest that, compared to childhood, adolescence is a crucial developmental period characterized by a maladaptive shift in the use of emotion regulation, with an increase in the use of maladaptive strategies in detriment to the adaptive ones [10]. From a neuroscientific perspective, irritability has been defined as an "aberrant responding to frustrative non-reward and threat" referring to the emotional state characterized by the abnormal increase in activity and aggression when an objective cannot be fulfilled [11]. Frustrative non-reward is included under the negative valence system of the RDoC matrix. Biological underpinnings of these deficits include decreased activation of striatal and frontal regions in response to frustrative non-reward and altered amygdala response modulation in response to threat [11]. These alterations underlying emotional and behavioural dysregulation linked to irritability also affect the cardiac-respiratory output via the autonomic nervous system [12].

The most used scale to measure paediatric irritability in clinical trials, the ABC-C, is a questionnaire for caregivers assessing irritability in intellectual and developmental disabilities. These characteristics limit translation of findings to clinical populations without cognitive impairment and to adolescents, for whom patient report of symptoms is preferred. New instruments targeting irritability, such as the Affective Reactivity Index (ARI) and youth- and parent-reported versions, have shown promising results for assessing irritability in research settings [13]. A clinician-rated version of this instrument (CL-ARI) has also shown good psychometric properties for assessing behavioural and mood components of irritability across diagnostic groups [14], which makes it a good candidate for use in clinical trials. The emotional, behavioural and autonomic dysregulation (EBAD) linked to irritability, which can be empirically measured, would also be a relevant target for treatment outcome and stratification [12].

In the case of DMDD, stimulants, atypical antipsychotics and serotonergic antidepressants have been tested, although data are still too scarce to guide treatment recommendations [15]. There is also some evidence that in particular disorders some other medications may be of help, such as stimulants for irritable dysregulated children with ADHD or ODD/CD [16]. However, in regular psychiatric practice, second generation antipsychotics are the more common treatments for children with severe irritability regardless of the respective mental disorder [17]. The wide use of these medications is not supported by clinical trials, carries potential for adverse events, and there is no specific information available on appropriate doses, treatment duration or expected outcomes.

Given the high prevalence of irritability in paediatric clinical settings, its associated clinical burden, and the frequent co-occurrence across diagnoses, a pragmatic symptom-based approach could be appropriate for the study of specific interventions for irritability and for designing transdiagnostic trials towards this end. These trials should consider including sensitive developmental periods, such as adolescent years, using validated treatment outcome measures, and allow sufficient follow-up to provide information on the clinical utility of medication approaches. It is still too common for clinicians to use a personal trial-and-error approach without the support of evidence-based information. New innovative treatment approaches for developmental psychiatry should be designed to answer these relevant clinical questions.

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Compliance with ethical standards

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