Comments on the proposal for inclusion of methylphenidate on the WHO model list of essential medicines for children and adolescents with attention-deficit/hyperactivity disorder

The complexity of the everyday patient raises concern of including methylphenidate on the WHO Essential Medicines List (1).

ADHD is characterized by core symptoms of hyperactivity, impulsiveness and attention deficits. We acknowledge that methylphenidate may ease core symptoms in the short term. However, when assessing a child or adolescents with ADHD, we need to look beyond these main features, as more than 80% of patients will also have one or more interacting co-morbidity (2,3). Of these, co-occurring insomnia, OCD, tics, depression, anxiety, oppositional defiant disorder and autism spectrum disorder are common (3–6). This means that having to treat a patient with ADHD, who presents with a complex profile of intertwined symptoms, is rather the rule than the exception in everyday clinical work.

Unfortunately, the evidence for treating co-morbidity in the context of ADHD is extremely limited. Clinical trials on ADHD tend to exclude these complex patients, and therefore majority of scientific literature does not reflect the everyday patient (7–9) . Despite the limited evidence, there are signs of concern that methylphenidate has a negative impact on patients with co-morbidity. The European medicine agency (EMA) published a report in 2009 underlining that methylphenidate has the potential to induce or worsen co-occurring psychiatric conditions in children and adolescents with ADHD (10). Here, EMA specifically mentions psychotic or manic symptoms, depression, aggressive behavior, suicidal tendency, tics, anxiety and bipolar disorder. Therefore, EMA recommended taking psychiatric co-morbidity into account when prescribing methylphenidate, and screen for emerging or exacerbation of existing psychiatric conditions in the young population, especially following long-term use (10). Apart from the above mentioned, methylphenidate is also known to induce and worsen sleep problems (11,12), as well as potentially induce OCD symptoms in youth (13). Methylphenidate has displayed opposing effects across age groups, as it may improve anxiety symptoms in adults, whereas long-term methylphenidate treatment in the young population can worsen anxiety symptoms later in adulthood (14).

On this note, the product characteristics cannot simply be taken at face value. A Cochrane systematic review of adverse events associated with methylphenidate treatment in non-randomized studies—including data from over two million children and adolescents with ADHD—found substantially higher rates of anxiety, sleep difficulties, tics, sadness, and decreased appetite compared to those reported

in the official Summary of Product Characteristics from both Denmark (15), the UK (16), and the USA (US Food and Drug Administration, FDA) (17,18)

Collectively, the limited evidence prevents us from knowing the full implications of both short - and long-term methylphenidate treatment for patients with ADHD, who simultaneously present other challenges. The aim is to treat one psychiatric disorder (e.g. ADHD), however as methylphenidate is likely to affect a wide range of psychiatric conditions, we might instead end up worsening the overall symptomatic profile, thus potentially leaving the patient worse off than to begin with. Due to the complexity of the clinical presentation, it may be uncertain if this deterioration in the state of the patient reflects the course of the disease or rather a medication-induced problem. Therefore, treating a child or adolescent with ADHD using methylphenidate is not necessarily a straightforward approach, as other intertwined symptoms can counteract the benefits. We are in high need of further studies on the matter, before we can ensure that non-maleficence is not being (unintentionally) practiced.

As the WHO Model List of essential medicines is to contain medications considered to be the most effective and safe, we argue against the inclusion of methylphenidate on this list. We currently do not know if methylphenidate is indeed a safe choice for young patients with ADHD and co-morbidities, who are so frequently seen in clinical practice.

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