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RESEARCH

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Bioethical evaluation of methylphenidate and atomoxetine for pediatric ADHD and cognitive enhancement

Enrique Burguete[1,2,3], Luisa Peydro[1,3] and Ignacio Ventura[1,3,4*]

Abstract

Background This article presents a bioethical analysis of the use of Methylphenidate and Atomoxetine, exploring their roles as cognitive enhancers and therapeutic agents for Attention Deficit Hyperactivity Disorder (ADHD).

Methods The analysis centers around the principle of non-maleficence, examining the ethical implications of causing harm in the pursuit of cognitive enhancement and therapeutic benefits. It delves into the blurred boundaries between therapy and enhancement and the challenges of defining "necessary harm" in these contexts.

Results When used for cognitive enhancement rather than therapeutic purposes, methylphenidate challenges the concept of "necessary harm," raising ethical concerns about seeking improvement at the cost of potential adverse effects. The very notion of neurocognitive enhancement remains controversial in the absence of a clinical pathology. In pediatric ADHD, there is a significant lack of long-term data on both therapeutic benefits and adverse effects beyond 30 weeks of treatment. Clinical trials have highlighted safety concerns, as methylphenidate has been linked to sleep disturbances, anorexia, nervous conditions, and, in rare cases, cardiac events. Additionally, exposure during pregnancy may pose risks of congenital malformations. While atomoxetine generally has minor side effects, occasional reports of suicidal tendencies warrant caution.

Discussion The article discusses the philosophical and ethical underpinnings of human nature, individual autonomy, and the pursuit of enhancement, drawing on historical perspectives from figures like Julian Huxley and contemporary transhumanist ideals.

Conclusion The study advocates for a cautious approach to cognitive enhancement, emphasizing the preservation of the individual's well-being over performance gains. In the context of ADHD treatment, it calls for an ethical examination of the long-term effects of Methylphenidate and Atomoxetine use in children and adolescents, recommending a preference for behavioral treatments when possible. Pediatric ADHD: There is a notable scarcity of data regarding the prevalence of therapeutic benefits and/or adverse effects in treatments exceeding 30 weeks. Furthermore, clinical trials concerning its safety and the lack of long-term data compromise the principle of non-maleficence, as we know that the use of Methylphenidate can lead to sleep disorders, anorexic conditions, nervous disorders, and has occasionally been associated with cardiac events. It also has effects on pregnancy that can lead to malformations in offspring. And although the unwanted effects associated with atomoxetine are generally minor, suicidal tendencies have been occasionally reported.

*Correspondence:
Ignacio Ventura
ignacio.ventura@ucv.es
Full list of author information is available at the end of the article

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder in children and adolescents, characterized by cognitive and behavioral patterns affecting cognitive, educational, and occupational functioning (ICD-11, 6A05). The disorder is marked by increased impulsivity, activity, and distractibility, leading to challenges in self-control, adherence to rules, and adaptation to social and academic settings. ADHD's prevalence ranges from 5 to 10%, with a higher incidence in boys, primarily the hyperactive-impulsive subtype [18]. Its multifactorial etiology involves genetic, neurochemical, and environmental factors [19].

Children with ADHD exhibit impairments in memory, emotional expression, and executive functions, impacting their academic performance and potentially leading to academic underachievement [32]. Neuroimaging studies have linked ADHD to structural brain differences, particularly in the prefrontal cortex, basal ganglia, and cerebellum. However, these differences do not necessarily indicate functional deficits [23].

The diagnosis of ADHD relies on clinical criteria outlined in the DSM-5, including symptoms like excessive restlessness, impulsivity, and inattentiveness. Dysregulation in neurotransmitters dopamine and norepinephrine is believed to underlie these symptoms, with dopaminergic pathways associated with hyperactivity and impulsivity and norepinephrine pathways affecting cognitive and emotional symptoms [11].

The long-term side effects of ADHD medications, such as Methylphenidate and Atomoxetine, are uncertain, particularly when administered during significant neurobiological changes in childhood and adolescence. The potential existence of these effects requires a bioethical analysis mindful of the principle of non-maleficence [4].

The use of medications is rational when "patients receive appropriate medications, in doses that meet their individual requirements, for an adequate period of time and at the lowest cost both to them and to the community. Irrational use occurs when one or more of these conditions are not met" (Van den Bogert, Mestrinaro, & Weerasuriya).

"Good prescribing practices" must include choosing the best treatment in terms of efficacy and cost, the best way to administer it, adequate patient information for consent, and pharmacovigilance regarding potential unwanted effects. They should avoid polypharmacy, the use of medications that do not correspond to the best therapeutic alternative, prescribing medication based on an incorrect diagnosis, prescribing to please the patient, omission of non-pharmacological measures, and the use of medications with questionable efficacy and/or safety. Good pharmaceutical practice, for its part, requires longitudinal clinical trials and their enrichment with information reported from medical practice.

The absence of longitudinal clinical trials, potential overdiagnosis and difficulty in reaching a definitive diagnosis, the existence of psycho-pedagogical treatment alternatives (often overlooked because they require more effort and time) constitute, therefore, bioethical objections to consider prior to prescribing methylphenidate and atomoxetine for ADHD treatment in minors. These same factors also make the use of these drugs for neurocognitive enhancement controversial.

This analysis aims to avoid the increasing trend of consequentialist and utilitarian bioethics, which prioritize efficiency, performance, and other extramoral values. Instead, it seeks to assess biomedical practices concerning the fulfillment and perfection of individual human nature.

We have dismissed consequentialism due to its inability to explain the experience of duty as it manifests in naïve moral consciousness, where responsibilities arise toward those affected by our actions or omissions. Actions that, by their nature, intention, context, or consequences, fail to fulfill this responsibility are deemed "bad" and morally reprehensible, even if they may appear convenient in extramoral terms.

The principle of responsibility reminds us that no strategy aimed at maximizing goods can freely dispose of all modes of action. However, consequentialism abandons this moral limit by subordinating the ethicality of our actions to the sole imperative of efficacy. This approach requires complex and exclusive knowledge, which, being inaccessible to most, transfers ethically contentious decisions to supposed experts in strategic planning. As Hegel pointed out, this could justify exonerating an arsonist from responsibility for burning down a house by limiting the purpose of their action to setting fire to a small pile of hay, disregarding the broader consequences of their act (§119, *Hegel*).

Moreover, consequentialism confronts the moral agent with two equally problematic scenarios: either it absolves them of responsibility for the secondary

consequences of their actions, or it holds them accountable for each and every one of these consequences, insofar as their foresight allows. The latter scenario, while theoretically plausible, demands unattainable assumptions: that the moral agent knows all possible global states of the world that could arise at any point following their action, that they can compare and rank all those states unequivocally, and that they can assess the contribution of each of their actions and omissions to achieving those outcomes. Since this is impossible, consequentialist judgment is reduced to probabilistic calculation—an unstable foundation for ethical decision-making (*Shiller, p. 158*).

In the context of the doctor-patient relationship, a similar question arises: is the prescription of methylphenidate or atomoxetine the spark that ignites the haystack, or the cause of the fire? Without robust longitudinal studies, these treatments might rely more on conjecture than certainty. One could appeal to contexts aimed at optimizing performance—whether educational or professional—as justification for these choices. However, in bioethics, the person is the context: an absolute end that must not be instrumentalized. When health is at stake, relying on speculative bets to justify such interventions appears to rest on an ethically precarious foundation.

The principle of non-maleficence rests on the recognition of the patient's personal dignity—particularly when its foundation extends beyond the limitations of principlism, drawing instead from the enriching elements of personalism and virtue ethics.

Principlism, in effect, lacks a robust foundation for its principles and fails to establish a clear hierarchy among them. As a result, its principles often become mere tools to legitimize controversial medical decisions. Personalism, by contrast, structures its principles around a central category: the concept of the "person," defined as a corporeal, spiritual, and free being whose biological, psychological, spiritual, and social components form a substantial unity, not a mere accidental conjunction. For personalist bioethics, what happens to the body affects the whole person, and what is done to one part of the body impacts the entire organism.

Personalist bioethics draws on philosophical personalism to articulate its "principle of totality" or "therapeutic principle," which holds that it is permissible to intervene in one part of the body only when there is no other way to heal the whole body—or, in other words, the whole person. Furthermore, such an intervention must meet the following criteria: the informed consent of the patient, a reasonable expectation of success, and the impossibility of curing the whole person without the intervention.

Virtue, alongside norms and the idea of the good, constitutes one of the pillars upon which we aspire to sculpt our best selves. The pursuit of the good motivates adherence to the norms and duties that, in practice, underpin virtuous behavior. A bioethics based on virtue thus emphasizes the moral quality of the agent and their intentions, rather than focusing solely on the consequences of their actions. However, in the context of a medical ethos as fragmented as the current one, virtues must translate into principles or norms that guide the physician's actions. Otherwise, a disparity of criteria may arise, leading to comparative grievances and injustices.

Principlism, personalist bioethics, and virtue ethics collectively reveal the mutual interconnection between the good, the norm, and virtue. It is, therefore, appropriate to conceive of them as complementary approaches in addressing both motivations and obligations [1]. For instance, prudence would demand that, before prescribing methylphenidate and atomoxetine for the long-term treatment of pediatric ADHD, non-pharmacological psychopedagogical alternatives be thoroughly explored.

ADHD diagnoses have risen significantly, and treatment options include stimulant drugs like Methylphenidate and non-stimulants such as Atomoxetine. The moral relationships between healthcare professionals and children with ADHD significantly influence treatment goals and methods. Even with noble intentions, such as enhancing academic performance or alleviating attentional deficits, utilizing anything available may not be justified. The moral nature of actions and omissions in healthcare should not be exclusively evaluated based on extramoral outcomes, particularly in matters of individual health.

The Principle of Non-Maleficence: In 1978, the publication of the "Belmont Report" [10] established the principles intended to address ethical conflicts inherent in clinical research, particularly in experiments involving human subjects. The initial principles of respect for persons, beneficence, and justice were subsequently redefined and expanded upon by Beauchamp and Childress to extend their applicability to healthcare ethics [2]. These principles were definitively articulated as autonomy, justice, beneficence, and non-maleficence. Perhaps the most formidable challenge posed by these principles resides in the discord surrounding their hierarchy. The liberal tradition prioritizes the right of moral agents to make decisions predicated on their own values and personal beliefs regarding any intervention they may undergo. Consequently, it categorically prohibits imposing anything on others against their wishes, regardless of any criteria. Conversely, in the perspective of Diego Gracia [14], the principles of non-maleficence and justice hold a higher rank than the other two. Specifically, the

principle of non-maleficence extends beyond the Hippocratic imperative of "primum non nocere" and prohibits inflicting harm upon the patient, even when the patient may request it. Moreover, it takes precedence over the principle of beneficence by stipulating that, in the presence of "necessary harms" associated with a treatment, these harms should never outweigh the expected therapeutic benefit.

This study aims to assess the pharmacological treatment of ADHD in children and adolescents, with a particular focus on its application as cognitive enhancement in the absence of medical necessity. Grounded in the bioethical principle of non-maleficence, the primary objective is to scrutinize the impact of treatment. Secondary objectives encompass elucidating the active ingredients and mechanisms of action of Methylphenidate and Atomoxetine, categorizing their prolonged beneficial and adverse effects, and exploring their utilization as cognitive enhancers.

Materials and methods

The general objective of this study is to analyze, through the lens of the bioethical principle of non-maleficence, the use of methylphenidate and atomoxetine for cognitive enhancement in the treatment of pediatric ADHD.

The research methodology involved a conceptual analysis of relevant bioethical paradigms, including principlism, virtue ethics, and personalist bioethics, with a specific focus on their application to the non-maleficence principle. This was complemented by a critical review of the literature addressing the ethical implications of pharmacological interventions for ADHD in children.

No specific objectives were outlined, as the focus was placed on a comprehensive ethical analysis rather than a systematic investigation of discrete hypotheses or narrowly defined research questions. While distinctions between consequentialism and virtue ethics were explored in the introduction to provide theoretical context, these aspects were not directly addressed in the results section, as they primarily served to establish the analytical framework.

To achieve our research objectives, we conducted a comprehensive narrative review, encompassing randomized clinical trials and observational studies. Our primary focus was on investigating the pharmacological utilization of Methylphenidate and Atomoxetine as treatments for Attention-Deficit/Hyperactivity Disorder (ADHD) in pediatric populations. Our review encompassed studies published from January 2017 to May 2022.

Initially, a search of 44,987 articles was performed on PubMed. We systematically excluded studies characterized by low or exceptionally low levels of evidence. Furthermore, studies involving populations with comorbid conditions other than ADHD and participants who were of legal age, except when related to cognitive enhancement, were also excluded from consideration.

We identified and selected 66 relevant articles for inclusion in our review, with 43 specifically focusing on Methylphenidate and 23 on Atomoxetine.

Despite the advantages of the narrative approach, such as its ability to integrate complex bioethical perspectives, it is important to acknowledge its limitations. The lack of standardized protocols, and the absence of quantitative analysis may limit the replicability and generalizability of the conclusions. These limitations were addressed through an effort to incorporate multiple theoretical perspectives and detailed ethical analyses, strengthening the validity of the reflections presented in this study.

Results

Atomoxetine and Methylphenidate in the Treatment of ADHD: Attention-Deficit/Hyperactivity Disorder (ADHD) represents a prevalent neuropsychiatric condition in children and adolescents, often necessitating medical intervention. The scientific literature has extensively investigated the usage of medications like Atomoxetine and Methylphenidate in managing this disorder, documenting both their advantages and adverse effects.

Methylphenidate stands out as one of the most frequently employed medications for ADHD treatment. Multiple studies have demonstrated its efficacy in ameliorating core symptoms such as inattention, hyperactivity, and impulsivity [15]. Beyond its influence on core symptoms, Methylphenidate has exhibited the capacity to enhance patients' quality of life, social functioning, and academic performance [31, 33].

Nevertheless, Methylphenidate's application in ADHD treatment has also been associated with adverse effects. These effects encompass insomnia, diminished appetite and weight, nervousness, tick development, heightened heart rate, and increased blood pressure, among others [5, 13]. Furthermore, gestational health is a concern for the adult female population; however, pregnancies also occur, occasionally and with added risks, among the pediatric and adolescent population. In this context, it has been observed that Methylphenidate can traverse both the blood–brain barrier and the placenta, posing a significant risk of congenital malformations in offspring when pregnant women are exposed to Methylphenidate [6].

Atomoxetine as a medication with a high safety profile and few adverse reactions, which underpins its widespread contemporary utilization [26]. However, it is important to recognize that the lower incidence of adverse reactions may be attributed to its shorter period of usage since 2008, as opposed to Methylphenidate's

Table 1 Summary comparison of methylphenidate and atomoxetine in adhd treatment: efficacy, adverse effects, and safety profiles: It is important to note that side effects are indicative and may vary in intensity and duration. Additionally, the need for further research, especially in the case of Atomoxetine, regarding long-term adverse effects in children and adolescents with ADHD is emphasized

Aspect	Methylphenidate	Atomoxetine
Efficacy in ADHD Symptoms	Effective in improving inattention, hyperactivity, and impulsivity [15]	Effective in addressing core ADHD symptoms [27]
Improvement in Quality of Life	Improves quality of life, social functioning, and academic performance [31, 33]	Improves various aspects: learning, family and peer relationships, cognitive function, executive function, social skills, and more [32]
Common Adverse Effects	Insomnia, diminished appetite and weight, nervousness, tick development, heightened heart rate, and increased blood pressure [5]	Mainly gastrointestinal (abdominal pain, nausea, or vomiting) and cardiovascular (minor increases in heart rate and blood pressure) [29], Fu, 2022)
Gestational Risks	Crosses the blood–brain barrier and placenta, associated with risks of congenital malformations in offspring of exposed pregnant women [6]	Limited data, apparently lower risk due to its safety profile; however, further research is needed
Safety Profile	Associated with over 60 years of use, with known and manageable risks [5]	Less time in use (since 2008), with fewer known adverse reactions, but continuous research is required [26]

over 60-year history of use. In addition to addressing core ADHD symptoms, Atomoxetine has demonstrated the ability to enhance various aspects of children's functioning, including learning, peer and family relationships, cognitive function, executive function, social skills, and more [28] (Rubio Morell) [32].

Common adverse reactions in children and adolescents receiving Atomoxetine treatment for ADHD are primarily gastrointestinal (abdominal pain, nausea, or vomiting) and cardiovascular (minor increases in heart rate and blood pressure), as illustrated in Table 1. These symptoms are linked to the inhibition of norepinephrine reuptake. Less frequent side effects encompass drowsiness, reduced appetite and weight, dizziness, fatigue, and, occasionally, suicidal tendencies. It is noteworthy that these side effects typically occur during the initial months of treatment and tend to diminish over time, typically remaining mild to moderate [29].

It is important to note that our review did not uncover clinical studies examining Atomoxetine treatment in children or adolescents diagnosed with ADHD over periods exceeding 24 weeks. Therefore, potential adverse effects within such a timeframe remain unknown.

Table 1 provides a comprehensive overview of two commonly prescribed medications for attention deficit hyperactivity disorder (ADHD) – Methylphenidate and Atomoxetine. The comparison highlights key aspects, including efficacy in addressing ADHD symptoms, improvements in quality of life, common adverse effects, potential gestational risks, and the safety profiles associated with each medication. By distilling relevant findings from scientific literature, this summary serves as a quick reference guide for healthcare professionals, aiding in informed decision-making when considering treatment options for individuals with ADHD.

Discussion

In the exploration of the bioethical dimensions surrounding the utilization of Methylphenidate and Atomoxetine within the framework of the principle of non-maleficence, a nuanced evaluation is essential. The deontological obligation to avoid causing harm is fundamental in medical ethics, yet the intricacies arise when confronted with the concept of "necessary harms" within healthcare interventions. While certain medical practices, such as surgeries and the administration of specific medications for cancer treatment, inherently involve a degree of harm, they are justified by their potential therapeutic benefits. Drawing parallels to these instances, this discussion delves into the critical question of whether similar ethical considerations can be applied to the use of Methylphenidate and Atomoxetine—both in the treatment of ADHD and as cognitive enhancers. Examining the delicate balance between therapeutic intent and potential harm, the assessment seeks to navigate the ethical landscape surrounding these psychostimulants.

Bioethical assessment of the use of methylphenidate and atomoxetine from the principle of non-maleficence

To comprehensively evaluate the employment of Methylphenidate as a cognitive enhancer, guided by the principle of non-maleficence, it is imperative to consider the deontological mandate of not causing harm to the patient through therapeutic actions or omissions. However, in the healthcare and pharmacological context, there exist instances of "necessary harms" that align with the intention to heal. For illustration, commonly referenced examples include surgical interventions and the administration of anticancer agents such as cyclophosphamide and vincristine, aimed at inducing apoptosis and reducing cancerous tumors. Both these instances involve the infliction

of harm due to its perceived lesser impact compared to the potential therapeutic benefit expected by the patient. This prompts inquiry into whether similar principles apply to the use of Methylphenidate and Atomoxetine in treating ADHD or as cognitive enhancers.

Regarding the use of methylphenidate as a cognitive enhancer

When the adverse effects linked to Methylphenidate use for neurocognitive enhancement are acknowledged and these effects do not align with therapeutic criteria, the concept of "necessary harm" becomes moot. However, it is noteworthy that the demarcation between therapy and enhancement remains elusive. In principle, therapeutic actions are geared towards reinstating the "naturalness" of organs afflicted by specific pathologies, while enhancement aims to "liberate" individuals from the confines of their inherent human nature. As per Spaemann, individuals are characterized as persons, distinct from mere representatives of their species, because they possess a nature—the human nature—as their distinct "way of being." However, humans are not inherently their "way of being"; they are not essences but instead conduct themselves in a manner aligned with their essence, which they perceive as a contingency they can distance themselves from ([30], pp. 78–80). This is precisely the essence of the freedom that characterizes rational beings, though with two nuances: first, this freedom is always a freedom of acceptance, never of denial, since there is no dignity in rejecting our own nature. Second, dignity does not depend on the fullness of reason that enables this freedom. Even when our reason is still developing, is limited, impaired, or has been irretrievably lost, we remain human and possess dignity.

Consequently, it is reasonable to assert that individuals are inherently destined to intentionally transcend their nature. The means employed to achieve this goal may, however, when taken to extremes, jeopardize that which is genuinely human.

The elusive nature of the issue lies in the fact that, by its cultural nature, humans also transform themselves each time they technically intervene in nature. To illustrate this, consider how the mastery of fire by *Eurasian Homo erectus* led to changes in their diet, originating the growth of their cranial capacity and consequently expanding their intellectual and spiritual resources. The plasticity of our central nervous system also demonstrates that our body actively participates in receiving technological and biomedical modifications [20].

However, until today, these enhancements resulted from actions aimed at adapting humans to their environment or restoring a damaged faculty. They did not respond to the desire to enhance human faculties beyond their constitutive naturalness. Today, technology allows transformations of the human body that go beyond necessity, such as cosmetic surgery without clinical indication, the use of drugs to enhance sexual performance in the absence of clear dysfunction [7], or neurocognitive enhancement [12].

Not every biochemical intervention without a medical prescription implies a manipulation of human identity or nature. However, there are psychotropic drugs and methamphetamines that cause changes in the most intimate aspects of personality when their consumption is not therapeutic but seeks states of euphoria, concentration, and/or performance beyond natural endowment [8]. The term "enhancement" applied to these interventions also defines a moral limit that, in the field of health policies, aims at treatments that are too expansive and exceed what a just system should provide to its population [17].

It is true, as noted by Robert Spaemann, that people are "something more" than our nature. We are not mere "cases" or "elements" of our species. We are not "essences" but "substances" with a specific essence that we perceive as contingency, being able to align ourselves with it or distance ourselves from it. Ultimately, people are praxis and not mere impulses. Therefore, it is not inaccurate to consider that humans are needed, by their own nature, to surpass their nature ([25], p. 39). The question is where, if at all, we place the limits on this surpassing that was already on the horizon of the Renaissance.

In fact, Pico della Mirandola asserted in the fifteenth century that man does not have a finished form and handles giving it to himself; that he is not subject to the natural laws that "determine" the rest of creatures so that he can shape his nature according to his free will [22]. However, Giovanni Pico referred to the ability that people have to sculpt their own statue through virtuous habits, that is, our ability to discipline our nature without subjugating or nullifying it, guiding it through our actions toward its fullness and perfection ([30], p. 191–92).

The transhumanist imperative of improvement articulated by Bostrom [3], on the other hand, is not teleological. Instead, it appeals to della Mirandola to justify the moral duty to surpass original nature, even when this entails transforming it into an already surpassed evolutionary episode. Or, without reaching such extremes, even if it involves medicalizing human life for the performance of everyday tasks (Dresler et al.).

This prophetic stance was precisely articulated by Julian Huxley, a biologist and eugenicist, and the first director of UNESCO. In the mid-twentieth century, he enthusiastically contemplated the potential to "raise man's present faculties to new heights and even the

discovery of new faculties." [16]. In contrast to the randomness of natural selection, characterized by Dawkins as a "blind watchmaker" [9], humans would shoulder the responsibility of consciously guiding evolution by delving into the roots of their biology to steer it towards a new, dominant, and superior form of life. Transhumanism envisions this new life form as an "enhanced human," which would subsequently evolve into a "more perfect" posthuman entity, endowed with greater intellectual abilities and complete control over emotions. This entity would relegate what is human to an evolutionary stage that has already been surpassed, with its only greatness, as Nietzsche believed, lying in being a bridge and not a goal: a transition and a decline [21].

In 2003, a report from the National Science Foundation expressed confidence that the convergence of sciences such as nanotechnology, biotechnology, cognitive sciences, and information sciences would allow for the revitalization of evolution to achieve a new type of progressing human with unlimited potential [24]. However, this ideal of progress does not refer to the perfection of the individual as a whole or the goal of a fulfilled life, but rather to the maximization of certain capacities that would enhance well-being and functionality. These human endowments include intelligence, memory, impulse control, foresight, patience, or humor, which enhancers consider limited by the body, the accident that accompanies the true human essence, which is consciousness.

Even without assessing the limitations of this dualistic anthropology, it is easy to see that the use of Methylphenidate as cognitive enhancement does not contribute to the progress of the complete person but only to their systemic functionality. This is clear in the distinction between the two possible types of progress based on the end to be promoted: those that make sense with their achievement and those that constitute "improvements" independently of it. The progress of the first type would include advancements in constructing a machine, as none of them would make sense if it never functioned. However, in the second type of progress, the telos of the process is already realized when the improvement begins. This is undoubtedly the progress that corresponds to the person understood as an end in themselves and not merely as a means, a function, or functionality for work; as "someone"—not as "something"—for whom progress implies maturation, unfolding, and a good life, and not just performance or functionality. It is not independent of their natural conditions.

For transhumanism, the person is conceived as a *pure cogito*, an incorporeal but computable process [7] that could well "shift" its support. Software, not hardware. The body, with its limitations, would be nothing but the original and non-chosen prosthesis, a fate or a prison in which self-awareness dwells due to natural endowment.

Spaemann's anthropological perspective can help unveil the aporias of this dualistic reductionism that confuses our substance with our essence and disregards the multidimensional nature of our being. These aporias are inherent in the concept of neurocognitive "enhancement" and, consequently, in the use of Methylphenidate and Atomoxetine for its achievement.

From an Aristotelian-Thomistic perspective, Spaemann explains that our human nature is constituted by the substantial union of soma, psyche, and pneuma. Here, pneuma refers to our "internal construction plan," the teleological structure or "intention" of our being. Our substantial form or soul in an Aristotelian sense. Consequently, our full personal realization requires more than the optimization of our emotional and intellectual capacities. It requires a human way of achieving that fullness we intentionally aspire to: the perseverant cultivation of virtue. Because all our acts are always and simultaneously physical, psychic, and spiritual/intentional. And although intentionality is connected to the psychic due to experience and cannot be repressed, it cannot be induced by psychic influences but precedes them ([30], p. 58). We can only consciously "want" something because there is a tendency towards it within us. Without this tendency, everything would be indifferent to us, and wanting one thing over another would be inconsequential. Experience is, therefore, a potential intentionality.

Spaemann also shows that the term "person" is a "substantial" expression characterized because it is not predicated "of" something but identifies something of which something is subsequently predicated ([30], pp. 78–80). The person is not solely defined by its essence and, therefore, is not reduced to its rationality, intelligence, or self-awareness. Rather, it is the individual substance that, in accordance with its rational nature, is capable of awakening these qualities that constitute its essence.

For Spaemann, the person is also one for whom impulse is not determinative. One who can conduct oneself one way or another concerning desires and acts of will ([30], p. 31). If one can do so—Spaemann adds—it is because one is "beyond" one is being, because one is not directly one's "experience" but the subject of one's experience. Therefore, one can look at oneself from outside, with the eyes of others, judging and "treating" oneself as one would treat another person, offering advice as one would with another person one is trying to influence ([30], p. 32).

In this sense, pharmacological interventions to overcome the neurocognitive limits of one's nature without clinical indication do not "enhance" the pediatric patient

qua person, that is, as a personal substance capable of self-government and freedom. Instead, it artificially alters their essence, preventing them from embarking on the path that would allow, while optimizing the functionality of the qualities inherent in their essence, to elevate their personal substance toward fullness. This path is nothing other than the cultivation of cardinal virtues, namely: prudence for proper deliberation, justice for following what is most correct for oneself and others, and fortitude and temperance to master impulses and lead one's nature, without subjugating it, to embody its best version.

The reduction of intelligence, memory, impulse control, foresight, patience, or humor to their objective function does not penetrate the 'inner side' of human experience. However, it does erase the distinction between what Aristotle referred to as Zen and what he called eu Zen (De anima 434b, 21); the distinction between 'life' and 'full life' ([30], p. 181).

In this sense, achieving a life that is not merely biological but also personal requires a certain mastery over oneself, a certain capacity for adaptation but also acceptance. Consequently, the idea of surpassing human qualities with the help of drugs does not imply a good for which the associated risks are acceptable. The person, and not their performance, is the good to be preserved.

The use of cognitive enhancers without medical indication exemplifies the increasing medicalization of life for carrying out the most ordinary tasks (Dresler et al.). This practice does not constitute therapy but rather an enhancement of capacities inherent to human beings. However, the very concept of enhancement and its ethicality remain ambiguous when applied to cognition. For instance, memory enhancement might be undesirable for someone burdened by painful childhood memories. On the other hand, slowing cognitive decline associated with aging—despite not being classified as a pathology by medicine—is ethically acceptable, even though it constitutes an enhancement. Its preventive nature could be likened to that of vaccines, which strengthen the immune system beyond the natural baseline of the recipient to prevent infections not yet contracted. Moreover, cognitive enhancers seem to yield better results in individuals whose normal levels of memory, attention, or concentration fall at the lower end of established curves (Daubner et al.). Thus, even without being considered therapy, their use in such individuals could serve as a balancing factor.

In any case, with this exception noted, the lack of longitudinal clinical trials regarding the long-term efficacy and safety of drugs with enhancing effects raises significant concerns about their alignment with both the principle of non-maleficence and the therapeutic principle of personalist bioethics. This principle invalidates the enhancing use of methylphenidate because alternative methods for improving memory and attention exist without administering drugs to the patient. Additionally, from a personalist perspective, if the person is viewed as an integrated whole, the enhancement of cognitive capacities should not cause insomnia, anorexia, or tics, let alone more severe but less frequent side effects. Finally, the principle is further violated because the reasonable hope of success remains questionable until long-term efficacy studies are available.

Regarding the Therapeutic Use of Methylphenidate and Atomoxetine: The existing literature has consistently indicated the effectiveness of both Methylphenidate and Atomoxetine in treating ADHD, with more immediate and discernible outcomes typically observed with Methylphenidate than Atomoxetine. Although both principles have associated adverse effects, evaluating the balance between risks and benefits through the lens of the principle of non-maleficence supports their usage, dismissing definitive ethical objections to their administration in children and adolescents. Most of these adverse effects are transient, and the therapeutic effects more than compensate for their occurrence. However, it is noteworthy that clinical trials span no more than 20 weeks, and scientific evidence concerning their long-term effects is lacking. This becomes particularly striking given that treatments in children and adolescents often extend over months and even years, a phase during which their brains undergo significant development, rendering prolonged administration of psychostimulants potentially impactful.

Consequently, in alignment with the deontological imperative of not causing harm, especially in young patients, it appears judicious to initially opt for behavioral treatments incorporating resources from psychoeducation over exclusive pharmacological interventions whenever feasible. This is especially crucial given the evidence suggesting the potential for overdiagnosis and overtreatment in children and young individuals with mild ADHD, for whom the benefits of psychostimulants are not definitively proven to outweigh the potential adverse effects of their administration. In fact, the World Health Organization (WHO) has excluded methylphenidate from its list of essential medicines, justifying this decision based on the scarcity of trials examining the benefits and adverse effects of its administration beyond three months.

Conclusions

Considering our extensive review of recent medical literature, several crucial conclusions within the framework of bioethics emerge:

1. Neurotransmitter Mechanisms: The principal active components, methylphenidate and Atomoxetine,

deployed in the treatment of ADHD exert their influence on the central nervous system's pivotal neurotransmitters, dopamine (DA) and norepinephrine (NA), consequently precipitating alterations in the cerebral cortex. Hence, their utilization during developmental stages should be judiciously reserved for cases characterized by severe symptoms.

2. Efficacy and Safety in Short-Term Treatments: Our analysis has established the efficacy of both Methylphenidate and Atomoxetine in treatments spanning less than 30 weeks, with most adverse effects manifesting in mild forms. However, the dearth of data concerning the prevalence of therapeutic benefits and/or adverse effects in treatments surpassing the 30-week mark is conspicuous.
3. Inappropriateness of Cognitive Enhancement: The deployment of Methylphenidate and Atomoxetine as cognitive enhancers is unequivocally deemed inappropriate. This determination arises from the contravention of the principle of non-maleficence, as the potential adverse effects significantly outweigh the anticipated advantages.
4. Principle of Non-Maleficence in ADHD Treatment: Furthermore, the administration of Methylphenidate and Atomoxetine infringes upon the principle of non-maleficence when employed in the management of mild or moderate ADHD cases. In instances characterized by severe ADHD, the decision to proceed with treatment should be meticulously evaluated on a case-by-case basis, taking into account the risk–benefit ratio associated with its implementation.

These overarching conclusions serve as a clarion call to underscore the ethical considerations that must serve as the compass for the utilization of these medications in the context of ADHD treatment and their prospective role as cognitive enhancers. Paramount among these considerations is the unwavering commitment to prioritize the well-being and safety of individuals, thereby ensuring that ethical imperatives guide decision-making in this realm of medical practice.

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Authors' contributions
All authors read and approved the final manuscript. - Ignacio Ventura contributed to the conception and design of the study, data collection and analysis, and drafting of the manuscript. - Enrique Burguete supplied guidance, oversight, and critical revisions to the manuscript. - Luisa Peydros helped with data collection and supplied minor contributions to the manuscript.

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Data availability
All data sources, articles, and materials referenced in this literature review are publicly available in reputable scientific databases and publications. Any specific references or datasets used in this review can be accessed through the respective sources cited in the manuscript.
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Universidad Católica de Valencia San Vicente Mártir, Valencia, Spain. [2]Faculty of Veterinary and Experimental Sciences, Valencia, Spain. [3]Bioethics Observatory, Valencia, Spain. [4]Faculty of Medicine and Health Sciences, Valencia, Spain.

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