REEVALUATING ADHD AND ITS FIRST-LINE TREATMENT: INSIGHTS FROM DSM-5-TR AND MODERN APPROACHES

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Abstract

Is Attention Deficit Hyperactivity Disorder (ADHD) a "brain disorder"? Should it be managed regularly with stimulant drugs? This article critically examines the evolving biomedical discourse surrounding these questions through a close inspection of the latest edition of the influential psychiatric manual - the DSM-5-TR - as well as additional authoritative sources (e.g., previous DSM editions, consensus statements, FDA communications). The DSM-5-TR acknowledges that "no biological marker is diagnostic for ADHD" and that "meta-analyses of all neuroimaging studies do not show differences between individuals with ADHD and control subjects." The authors of the DSM-5-TR, therefore, conclude that "until these issues are resolved, no form of neuroimaging can be used for diagnosis of ADHD." These statements, along with biases in the neuroimaging literature and additional empirical evidence presented in the article, challenge popular myths about the neurobiological basis of ADHD. Similarly, common beliefs about the first-line treatment of ADHD with stimulant drugs are being increasingly questioned today. For instance, the DSM-5-TR's section on Stimulant-Related Disorders introduces a new diagnostic entity named: Stimulant-Induced Mild Neurocognitive Disorder. This addition aligns with a recent FDA Drug Safety Communication for "all prescription stimulants," which highlights longstanding concerns regarding the safety of medications prescribed to millions of diagnosed individuals, primarily children. The FDA now mandates that "the Boxed Warning, FDA's most prominent warning, will describe the risks of misuse, abuse, addiction, and overdose," emphasizing that such "misuse and abuse of prescription stimulants can result in overdose and death." In light of these challenges to the biomedical discourse, this article offers a neurodiversity-oriented alternative. Using evolutionary principles and historical context, it argues that most cases of ADHD fall under the DSM's socio-philosophical category of "conflicts that are primarily between the individual and society" (similar to homosexuality, which was removed from the DSM in 1973), and are therefore "not mental disorders".

Key words: ADHD, DSM-5-TR, FDA, neurodiversity, neuroimaging, stimulant medications, biomedical model

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Introduction

In March 2022, almost a decade after the publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the American Psychiatric Association (APA) published a comprehensive Text Revision of this influential manual – the DSM-5-TR (APA, 2022a). The primary revisions of this latest edition are summarized in designated fact sheets issued by the APA (APA, 2022b), but these sheets do not contain information regarding Attention Deficit Hyperactivity Disorder (ADHD) – the most common neurodevelopmental diagnosis in children (Vos et al., 2017). The current article employs a historical

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perspective and offers a close read of the DSM-5-TR, which brings forth a substantial insight: The common biomedical discourse surrounding the neurobiological foundations of ADHD and its first-line pharmacological treatment (ADDitude Editors & Silver, 2021; Kooij et al., 2019) warrants reconsideration.

Is ADHD a 'brain disorder'?

Like the previous edition of the manual, DSM-5-TR provides readers with a general statement that essentially could fit all psychiatric diagnoses. "*No biological marker is diagnostic for ADHD*", it says clearly (APA, 2022a, p. 73). However, the new edition goes an extra mile and elaborates on the precise state of the current literature on this topic. "Although some neuroimaging studies have shown differences", the manual explains, "meta-analysis of all neuroimaging studies do not show differences between individuals with ADHD and control subjects". The authors of the DSM-5-TR therefore conclude that "until these issues are resolved, no form of neuroimaging can be used for diagnosis of ADHD".

Although experienced neuroscientists are probably not surprised by the aforementioned revision of the DSM-5-TR, it does seem to deviate from the common biomedical-oriented discourse about ADHD - a discourse often referring to the disorder as a chronic neurogenetic deficit (Barkley, 2012), sometimes using straightforward phrases such as "brain disorder" (Biederman & Spencer, 1999). In fact, the very term of 'ADHD' is fairly new. According to a recent article by the medical historian Matthew Smith (2024), the modern concept of ADHD only came into prominence in the late 1950s due to geopolitical and domestic pressures on the US (Smith, 2024). Formally, the medical label we use today (which emphasizes attention difficulties), was only introduced in 1980, when the third edition of the psychiatric manual (DSM-III) presented the label 'Attention Deficit Disorder'. According to the authors of this edition, this new label of Attention Deficit Disorder was formulated to replace multiple previous labels, of which many implied that the person has a (physical) problem in their brain. These previous labels included: 'Minimal Brain Damage, Minimal Brain Dysfunction, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction" (APA, 1980).

Historically, the removal of the direct reference to the 'brain' from the formal label occurred even earlier, in 1968, when the previous edition of the manual (DSM-II) presented the label 'Hyperkinetic Reaction of Childhood'. However, in practice, the various editions of the DSM maintained this idea that ADHD is essentially a neurobiological condition by placing this condition within the manual section on *neurodevelopmental disorders*.

Although numerous critics challenged this conceptualization of ADHD throughout the years since its establishment in 1980 (e.g., Ärmstrong, 2017; Moncrieff & Timimi, 2010; Ophir, 2022b; Saul, 2014; Timimi et al., 2004), the 'scientific consensus' seemed to support it unequivocally. In 2002, a large consortium of experts led by Russell Barkley even published an "International Consensus Statement" on this matter (Barkley, 2002). According to this statement, there is "overwhelming" evidence that ADHD is a genuine disorder with traceable bio-neurological markers and genetic foundations. Correspondingly, ADHD is repeatedly depicted by leaders of the field as an objective and chronic medical condition that should be managed regularly, preferably with stimulant medications (American Academy of Pediatrics, 2011; Daley, 2006; Faraone, 2005). The recent European Consensus Statement from 2019 concludes that ADHD is "a neurodevelopmental and heritable disorder with a lifespan perspective: starting in childhood, persisting in adulthood until old age" (Kooij et al., 2019, p. 27).

To capture the essence of this biomedical view of ADHD, it is worth watching the recorded keynote lecture by Barkley (Barkley, 2012), the leader of the International Consensus Statement mentioned above. Following is a small segment from this lecture:

"You have a brain; the back part is where you

learn, and the front part is where you do... ADHD splits them apart... You can be the brightest kid in the world, not gonna matter. So you have a real problem on your hands... all of this in ADHD is due to neurogenetic deficits... Now, about 1 in 6 people might outgrow it, maybe it's 1 in 3, we're not sure yet, but the vast majority, two-thirds will continue to have ADHD in adulthood, and they need to view ADHD as the diabetes of the brain. It's a chronic disorder" (Barkley, 2012).

While many scientists and clinicians holding this 'brain-oriented' view of ADHD "as the diabetes of the brain" understand its conceptual and empirical limitations, lay persons might accept it as it sounds: a concrete physical brain impairment that can actually be seen in neuroimaging tools. In a representative article from 2021 by the editors of 'ADDitude' – a popular website dedicated to bringing credible information about ADHD to the public – the editors explain that "ADHD was the first disorder found to be the result of a deficiency of a specific neurotransmitter" (ADDitude Editors & Silver, 2021). They then list four specific brain regions that showed "impaired activity" and presented them as "truths about the ADHD brain that most people don't understand".

But are these "truths about the ADHD brain" really supported by the available scientific evidence? The answer, according to the DSM-5-TR that was cited above, is no. A large meta-analysis of 96 neuroimaging studies showed that there are currently no significant brain regional convergences in ADHD (Samea et al., 2019). In other words, the available research did not yield reliable and consistent brain differences between individuals with and without ADHD. This is aside from the publication bias found in the neuroimaging literature, which prevented contradicting studies (that did not match the governing, biomedical assumptions about the 'ADHD brain') from being published (Samea et al., 2019).

A second "truth about the ADHD brain that most people don't understand" is that the speculations regarding dysregulations in certain neurotransmitters in the brains of ADHD individuals had never received adequate scientific support (for a detailed review, see Chapter 6 of my book on this topic; Ophir, 2022a). This simple 'truth' is actually relevant to all psychopathologies (Breggin, 2016; Healy, 2015; Jucaite & Nyberg, 2012; Krishnan & Nestler, 2010). A notable remark that summarizes this 'truth' has been articulated by the former editor of the Psychiatric Times: "Like the legendary Count Dracula, who could be killed only by driving a stake through his heart, some myths seem almost immortal. For more than 8 years now, I have tried to drive a stake through the heart of two myths regarding the so-called chemical imbalance theory but with only limited success... As for the bogus chemical imbalance theory and its misattribution to the profession of psychiatry, it is time to drive the stake into its misbegotten heart" (Pies, 2019, pp. 9-11).

Without entering the dispute whether indeed psychiatry has always renounced the chemical imbalance theory, this quote captures the contemporary, mainstream view regarding the popular, yet probably wrong notion, as if mental disorders can be traced back to specific chemical imbalances in the brain. This unfounded notion has likely been promoted by companies and organizations with conflicts of interest, which did not always prioritize the well-being of individuals diagnosed with ADHD (Whitaker, 2005). Unfortunately, such conflicts of interest are common in medical and psychiatric research, often resulting in unwanted biases (e.g., Angell, 2009; Boutron & Ravaud, 2018; Jureidini & McHenry, 2022; Ophir & Shir-Raz, 2020; Ophir & Shir-Raz, 2022; Siena et al., 2023). Even physicians appointed to the DSM-5-TR panel or task force had conflicts of interest. According to a recent study published in the BMJ, approximately 60% of these physicians received payments from the pharmaceutical industry (Davis et al., 2024). Nevertheless, despite these biased efforts to influence or shape study outcomes, no conclusive evidence has emerged to prove that ADHD is a brain disorder. In fact, the current scientific consensus, as stated in the DSM, is that "*no biological marker is diagnostic for ADHD*", as stated in the DSM.

Should ADHD be managed regularly with stimulant medications?

Another overlooked bias in the neuroimaging literature discussed above relates to the first-line treatment for ADHD, that is the stimulant medications. A longstanding review found that many neuroimaging studies failed to consider (i.e., statistically control for) the expected effects of the medications for ADHD on the brain (Leo & Cohen, 2003). Since stimulants, like all psychoactive substances, cross the blood-brain barrier and impact on biochemical processes within the brain (Arnsten, 2006; del Campo et al., 2011), it is possible that some of the reported brain differences reflected the prolonged negative outcomes of the medications (Castner & Goldman-Rakic, 1999; Diaz Heijtz et al., 2003; Motaghinejad et al., 2017), rather than an 'ADHD brain'.

Nevertheless, despite this bias, and despite longstanding and intense debates over the efficacy and safety of the medications for ADHD (Coghill, 2019; Swanson, 2019), stimulant drugs are considered by experts and medical organizations as the pharmacological treatment of choice for ADHD (American Academy of Pediatrics, 2011; Bolea-Alamañac et al., 2014; National Institute for Health and Care Excellence, 2018; National Institute of Mental Health, 1998). Inevitably, the biomedical understanding of the disorder presented above (as reflected, for example, in the keynote lecture by Barkley) was followed by wide prescriptions of allegedly complementing biomedical treatments. Today, most individuals diagnosed with ADHD are prescribed or offered psychostimulant medications, such as methylphenidate (e.g., Ritalin) and amphetamines (e.g., Adderall) (Danielson et al., 2018; Visser et al., 2016).

To capture the essence of the biomedical perspective on the treatment-of-choice for ADHD, it is useful to revisit the previously mentioned keynote lecture by Barkley (Barkley, 2012). Here is how Barkley describes the role of the medications:

"What does this [previously cited view about ADHD] means for treatment? Teaching skills is inadequate. It won't work... all of this in ADHD is due to neurogenetic deficits and that means that medications are absolutely justifiable. After all, if you have a neurogenetic disorder, then neurogenetic therapies have a role to play in the disorder. And they do. 80% of people with ADHD will be on medications for some point in their life. And it's a good thing. It's the most effective thing we have. There are other things we can do but this is the most effective... It means that ADHD is the diabetes of psychiatry, it's a chronic disorder that has to be managed every day to prevent the secondary harms it's going to cause, but there is no cure for this disorder.

A similar, straightforward message appears in the website of the American Academy of Pediatrics: "As glasses help people focus their eyes to see, these medications help children with ADHD focus their thoughts better and ignore distractions" (The American Academy of Pediatrics Parenting Website, 2019). This idea makes sense from the biomedical point of view. If individuals with ADHD are experiencing an objective, chronic physiological condition that affects their brain biochemistry, then continuous treatment with pharmacological substances (similar to the approach for diabetes), seems quite reasonable. Allegedly, without such treatment, they may struggle to manage the symptoms and risks associated with this presumed brain deficit. "After all", as Barkley put it, "if you have a neurogenetic disorder, then neurogenetic therapies have a role to play" (Barkley, 2012).

Subtle cracks in this narrative can be seen in the substantial body of research challenging the efficacy and safety of these medications (for a comprehensive review see: Ophir, 2022a). And here too, a close reading of the DSM-5-TR might be informative. The sub-section of the new edition of the manual addressing the range of Stimulant-Related Disorders now presents a novel diagnostic entity named: A Stimulant-Induced Mild Neurocognitive Disorder (First et al., 2022). Whereas the previous edition mainly addressed the abuse, intoxication, and withdrawal components of stimulant use, the new edition acknowledges also the potential, longstanding implications of stimulant substances on the brain. These implications can be manifested in a range of mental disorders (e.g., psychotic, bipolar, depressive, anxiety, or obsessive-compulsive disorders; APA, 2022a), including ADHD-like symptoms (Molina et al., 2009), such as impairments in memory, learning, and executive functions (First et al., 2022).

Indeed, the main concern of this sub-section of the DSM revolves around illicit stimulant drugs (e.g., cocaine) that are abused without medical justification or supervised doses. However, medically prescribed stimulants (e.g., Adderall) were not excluded from this new diagnostic entity; nor should they as they fall under the same chemical category of "amphetamine-type substance" mentioned in the updated manual (APA, 2022a, p. 633). Moreover, both illicit and medically prescribed stimulants impact the brain directly, as mentioned above, and both have (also) a range of unwanted effects (Gould et al., 2009; Konrad-Bindl et al., 2016; Ophir, 2022c; Storebø et al., 2018; Zhang et al., 2023).

In a way, this (artificial) distinction between medically prescribed stimulants and illicit stimulants can be misleading, as implied recently by the Food and Drug Administration (FDA) of the US. On May 11, 2023, the FDA issued updated warnings about stimulant medications for ADHD (FDA, 2023) that undermined a common belief regarding their safety (Faraone, 2023). The FDA ruled that "even when prescribed to treat an indicated disorder, their use can lead to misuse or abuse" (FDA, 2023). Accordingly, the FDA now requires that "the Boxed Warning, FDA's most prominent warning... will describe the risks of misuse, abuse, addiction, and overdose consistently across all medicines in the class". This warning is crucially needed because, "misuse and abuse of prescription stimulants", in the FDA's words: "can result in overdose and death" (FDA, 2023).

Conclusions and viewpoint

Do the noticeable clarifications discussed in this article by the FDA and the APA - two highly influential medical authorities - signal a significant shift in the common discourse about ADHD and its first-line treatment? Only time will tell. Scientifically speaking, the four decades of research since the 1980s when the DSM-III first introduced 'Attention Deficit Disorder', did not yield reliable and clear biological markers that can be used for real-life clinical diagnosis. Currently, there are no reliable physiological measures for diagnosing ADHD, and actually, most physicians believe that this diagnosis is given often without proper medical justification (Davidovitch et al., 2021). If there were such solid physiological tests that could signify that the person has ADHD, these mistakes could have been easily avoided.

Despite the common biomedical discourse referring to ADHD as a chronic "brain disorder" or as "the diabetes of psychiatry", real-life diagnoses of ADHD rely on behavioral observations and subjective questionnaires and interviews, essentially, like all other psychopathologies. Indeed, some clinicians use more objective (yet, non-physiological) computer-based Continuous Performance Tests (CPTs), such as TOVA (Leark et al., 2007) or MOXO (Berger & Goldzweig, 2010), but these tests are considered even less reliable and less valid than the traditional diagnostic tools (Barkley, 2019). They produce poorer results than selfreport scales and they involve non-realistic tasks, which do not resemble daily behaviors. Surprisingly, even Barkley (2019) called to avoid using these tests in an article titled: "Neuropsychological testing is not useful in the diagnosis of ADHD: stop it (or prove it)!

In practice, ADHD is not exempt from the general diagnostic rule of the DSM, which states that: "in the absence of clear biological markers... it has not been possible to completely separate normal and pathological symptom expressions contained in diagnostic criteria" (APA, 2022a, p. 24). In contrast to the common biomedical view presented in this article, the promising biological revolution in psychiatry of the previous century has not lived to its expectations (Harrington, 2019; Moncrieff & Crawford, 2001). At this time, as articulated in a recent JAMA Psychiatry editorial, "we are standing at a precipice: our explanatory disease models are woefully insufficient, and our predictive approaches have not yielded robust individual-level predictions that can be used by clinicians" (Paulus & Thompson, 2019).

Critics of the biomedical view in psychiatry are continuously reminding us that (as of today) human behaviors and experiences cannot be reduced to a small number of biological elements (Rosenberg, 2006). Not only that this *biological reductionism* has negligible predictive value for clinical diagnosis, but it could lead to "diagnostic literalism" - a problematic perception of abstract and tentative human-drafted labels as concrete and real medical entities (Fried, 2021; Kendler, 2017). Instead, many contemporary psychiatrists and psychologists prefer to view mental health difficulties from a more complex ecological prism, as products of multifaceted interactions between a wide range of biological, psychological, interpersonal, and environmental factors (Engel, 1977; Lehman et al., 2017). In a way, simpler biomedically-inspired assertions, such as: "Johny behaves this way because he has ADHD", have very little clinical value or real scientific truth.

Furthermore, even if, one day, ADHD-like

behaviors are proven to originate from clear biological components, this alone would still not be sufficient for real-life clinical diagnoses. The fundamental *monistic approach* to the mind-body problem (that seems to be shared by most scientists) is that all human experiences, even the most amorphic ones, have some physiological manifestation in the brain. The very existence of brain differences between people is never enough to suggest that a given person suffers from a psychiatric disorder. Personality traits, such as introversion or extraversion may have neurological markers (e.g., Hsu et al., 2018; Nostro et al., 2018), yet these markers do not imply that one of these traits is a brain disorder.

This plain insight underlies the more contemporary discourse, which relates to ADHD (and additional conditions, such as Autism) through the prism of *neurodiversity* – the natural, non-pathological variations in personality and behaviors between humans (Armstrong, 2011; McGee, 2012; Moore et al., 2021). Humans naturally differ from one another. The fact that a person has an a-typical brain (or qualities for that matter) does not mean they have a disorder. The neurodiversity approach suggests that benign personality characteristics became mental disorders only today, in our modern world of ever-growing demands for sociability and productivity in schools and workplaces (McGee, 2012).

Moreover, neurodiversity is the foundation of what we often refer to as 'talent'. Individuals labeled as 'hyperactive' may also be seen as energetic, physically gifted, and adventurous. Similarly, those considered 'distracted' may possess strengths in associative thinking and creativity, depending on how we frame these characteristics. Correspondingly, critics of the biomedical view have begun to study the 'bright side of ADHD' (e.g., Abraham et al., 2006; White & Shah, 2006). Some scholars argued, for example, that the distractibility and impulsivity tendencies characterizing ADHD can take a positive form of courage, cognitive flexibility, fortitude, and resilience (Sedgwick et al., 2019). Others contended that many ADHD-type individuals are highly creative (Boot et al., 2017; Chrysikou, 2019), as they are capable of considering multiple aspects of a problem in a kind of a "lateral thinking that opens things up to big ideas" (Archer, 2015, pp. 128-129). Apparently, even the impulsivity and risk-taking qualities typically associated with ADHD are thought by some scholars to be valuable in certain, highly challenging contexts, such as entrepreneurship or the military (Lasky et al., 2016; Montes & Weatherly, 2014; Olinover et al., 2021; Rice et al., 2013; Wiklund et al., 2016; Wiklund et al., 2017).

A plausible theoretical explanation for this neurodiversity-oriented view about ADHD derives from evolutionary psychology. Hartmann, for example, theorized that individuals with ADHD-like traits can be thought of as "hunters in a farmer world" (Hartmann, 2019). In his view, risk-taking and impulsivity used to be virtuous personality strengths in historical huntergatherer societies. ADHD-type 'hunters' were probably the ones to monitor the environment for food and threats (distractibility) and to engage in abrupt, highrisk actions (impulsivity/risk-taking).

From this neurodiversity point of view, ADHD might be better conceptualized as a context-dependent condition, rather than an objective disorder of the brain. ADHD-like traits might have been preserved throughout the natural selection process because they contributed to the survivability of the individual, or of the species, in certain environments (e.g., battles and nature disasters) (Grossman et al., 2015; Shelley-

Tremblay & Rosen, 1996; Swanepoel et al., 2017). Therefore, nowadays, following the agricultural and the industrial revolutions, ADHD can be seen as sort of an "evolutionary mismatch" (Swanepoel et al., 2017), especially in childhood, as most schools do not fit the associative thinking and sensation seeking tendency of ADHD-type children (Ophir, 2022a).

Notably, the neurodiversity view holds even when the traits of the individual do not have distinct evolutionary or beneficial value. For example, gender identity and sexual orientation might have some neurological and genetic markers (e.g., Ponseti et al., 2007; Swaab, 2004), yet these markers are, by no means, indicative that something is wrong with homosexual or transexual individuals. Homosexuality is actually a fundamental example of the potential confusion between plain interpersonal differences dictated by natural neurodiversity and psychiatric disorders, as it once was mistakenly classified. Homosexuality has been removed from the psychiatric manual in 1973 (Drescher, 2015) and today, even those who insist that the 'homosexual brain' is different than the 'heterosexual brain' acknowledge that homosexuality should not be categorized as a psychiatric disorder.

It is therefore my view that the same grounding philosophical assumption should be laid in the debate over the validity of ADHD. To answer the question whether ADHD is a valid medical condition (let alone brain disorder), we need take a theoretical step backwards and define the basic philosophical assumptions that stand behind the conceptualization of mental disorders. In other words, we need to ask the fundamental questions underling humans' neurodiversity: Where does personal character end and a mental disorder begin? What makes certain human tendencies a valid psychiatric disorder?

All throughout history, humans have tried to understand and classify abnormal behaviors (Blashfield et al., 2014). From a philosophy of science point of view, the premise of this investigation - the null hypothesis (H0) as commonly referred to – should be the assumption that human beings are normal until proven otherwise (regardless of whether they are, for example, homosexual, energetic, or impulsive). In order to reject this null hypothesis and argue for an alternative hypothesis (H1), in which a cluster of behaviors constitute a psychiatric disorder, theorists must first prove that these traits are exceptionally deviant from normal human behaviors, meaning that they are at the extreme end of the human behavior spectrum. In fact, this is only the first criterion that must be met before subsequent criteria can be considered.

A conventional typology used to determine whether certain behaviors and tendencies constitute a mental disorder is the *Four D's criteria of psychiatric diagnosis*: Deviance, Dysfunction, Danger, and Distress (Davis, 2009). An in-depth exploration of these criteria in relation to ADHD is available in a comprehensive rebuttal of the biomedical narrative I published in 2022 (Ophir, 2022a). For the purpose of this article, I would like to bring forth only one (key) statement from the DSM, which warns us that: "socially deviant behavior (e.g., political, religious, or sexual) and conflicts that are primarily between the individual and society are **not** mental disorders unless the deviance or conflict results from a dysfunction in the individual" (APA, 2022a, p. 15, bold added).

It is therefore crucial we determine the exact source of the dysfunction in ADHD. Is it really an objective deficit within the individual (and rare deficit – to meet the fundamental criterion of Deviance)? Or is it simply, yet another mode of thought or personality trait (with both pros and cons, like all human traits), which stands in conflict that is "primarily between the individual and society". Experts who conclude that many ADHD cases actually fit this last category might therefore wish to reconsider ADHD as "not mental disorder", as instructed by the DSM. They might also think twice before prescribing them potentially addictive drugs, as judged by the FDA, which impact the brain directly and have multiple unwanted outcomes.

This does not mean that we should ignore the millions of children given this diagnosis today. These energetic and/or easily distracted children should receive the maximum support and compassion. We should, by no means, travel back in time, and return to label them with derogatory names, such as lazy or stupid. However, in the same breath, it might be a good idea **not** to lead them to believe that something is wrong with their brain or that they must use drugs regularly to 'manage their symptoms'. First, do no harm. Second, follow the actual science, not the myths that are common in the public discourse.

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