Exploring The Difference in Brain Responses Between Adult and Pediatric Patients of Anxiety Disorders to Different Classes of Medication

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Received October 10, 2024
Accepted December 16, 2024
Electronic access December 31, 2024

Anxiety disorders are becoming increasingly common among people recently. Both pharmacological and nonpharmacological treatment methods have been developed to address these anxiety disorders. Some classes of medication used for this condition are selective serotonin reuptake inhibitors (SSRI), benzodiazepines, and buspirone. SSRIs are considered first-line treatment for anxiety disorders. Benzodiazepines are the oldest class of medication used to treat anxiety disorders. Buspirone is used to treat anxiety disorders in the short-term. SSRIs are the first choice of drugs to combat anxiety disorders for all patients, but they display the most variability in brain responses between adults and children. Benzodiazepine and buspirone are rarely chosen as first responders, but they display little variability. Such differences cause increased susceptibility or emergence of new side effects, which are assumed to be attributed to the changing brains of children. This growth influences the threshold of brains for certain chemicals that medications interact with. These variabilities regarding responses to the various classes of medication are thought to be mostly due to the developing brains of the pediatric patients. The changing nature of these neurological pathways and thresholds can oftentimes display unexpected reactions in the form of increased susceptibility to side effects. However, this increase does not apply to all children with anxiety disorder, as there are other factors, such as genetics, that affect individual responses.

Keywords: anxiety, SSRI, benzodiazepine, buspirone, side effect

Introduction

The human brain isn't considered fully developed until 25 and continues to mature and fine-tune itself until this age. The continuous developments within children's brains also cause differences in the way children and adult brains function and their structure[1].

As a result, children and adults also respond to drugs differently from each other. However, this gap between these two age groups has been inadequately researched, leaving the question of how this actually happens, unanswered. The differences in neurological pathways and thresholds between children and adults illustrate that children aren't just small adults, indicating that the response of children to drugs should be different than that of adults. Stephenson explores the validity of this assumption. He found that oftentimes, differences in pharmacokinetics (how drugs move through the body) are mistaken for differences in pharmacodynamics (responses to drugs)[2]. And while there are a number of cases where the pathophysiology and "host" responses are different for children than adults, responses of adults and children to many drugs still have much in common, as the basic physiology and intended effects are identical for both.

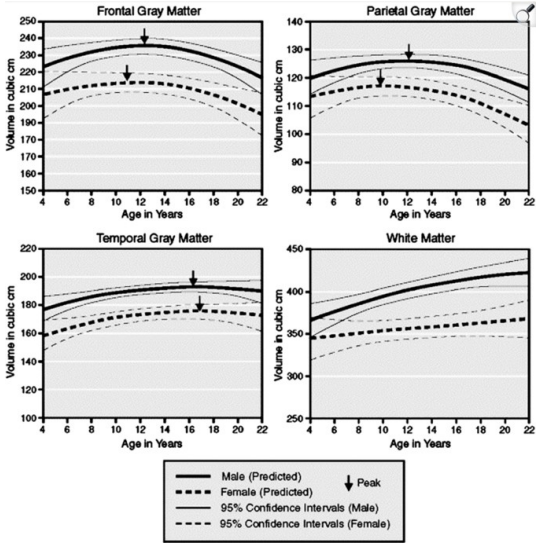

Fig. 1 Growth curves of gray and white matter volumes.

Amidst this discussion of pharmacodynamics, the differences in the presence of developmental differences between adults and

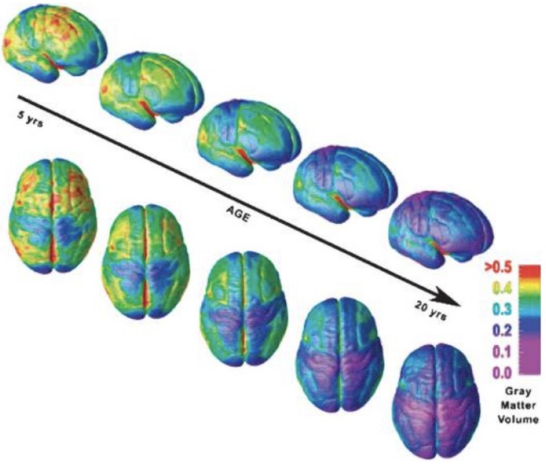

Fig. 2 Right lateral and dorsal views of the dynamic sequence of gray matter maturation over the cortical surface of the brain.

children highlight the possible need to address these differences when developing medication involving brain pharmacodynamics for conditions such as anxiety disorders.

Anxiety disorders involve complex interactions between brain regions, neurotransmitter systems, and physiological responses. Key mechanisms include neurotransmitter imbalances (serotonin, GABA, norepinephrine, dopamine) that arouse certain stress responses, brain circuitry (amygdala, prefrontal cortex) that are meant to regulate these stress responses, and the sympathetic nervous system that is triggered by anxiety, creating central responses to anxiety. Medications for anxiety work by modulating these mechanisms, either by balancing neurotransmitters, enhancing inhibitory neurotransmission, or reducing sympathetic nervous system activity. But these become difficult to control throughout all patients with the presence of differences in brain pharmacodynamics.

Even within non-pharmacological treatment methods, differences are present. Apart from medications, there are a number of therapeutic methods such as cognitive behavioral therapy, interpersonal psychotherapy, and even animal therapies that have been shown to be effective at treating mental disorders[3]. Research by the National Institute of Mental Health in 2024 reveals the effectiveness of cognitive behavioral therapy (CBT) within children[4]. Children with anxiety disorders displayed overactivation in many regions of the brain such as the amygdala (controlling fear, anxiety) and the frontal & parietal lobes (important for cognitive and regulatory functions). And among these child patients, those with continued CBT treatment were shown to display significant decreases in anxiety symptoms and improved functioning compared to those without continued CBT treatment. This study shines light on brain circuits linked to clinical improvement, which could be targeted to enhance treatment outcomes, especially for the children that didn't initially respond to CBT as significantly.

As these studies reveal, treatment methods for mental disorders, even the non-pharmacological methods, tend to have varying results and degrees of effectiveness between adults and children as adults did not display such variation in response to CBT. Previous studies have uncovered the overarching question of how differently, if at all, children respond to medications in general when compared to adults. The aim of this study is to investigate the possibility of such differences between children and adults regarding their response to the various classes of medication for anxiety, a mental disorder that has been rapidly rising in occurrence in recent years[5].

Methods

For our review on how different classes of drugs affect the brains of children ages 6 to 17 compared to adults, we used a systematic approach: We developed a protocol for a detailed outline for our methods and objectives. This allowed for smooth advancement of our review and prevented facing roadblocks midway through the review that would hinder progress. We also defined a clear search strategy to create an inclusion criteria for studies that we would use, ensuring usage of only quality articles from a relevant time period that was also relevant to our topic and peer reviewed by others. We then analyzed the quality of the studies to synthesize the evidence we have gathered and interpret the findings. The studies and articles we gathered data from and analyzed consisted of controlled clinical trials, bayesian analyses from abandoned trials acquired from deep searches with keywords (SSRI, BDZs, buspirone, developmental differences, pharamcodynamics), and other pharmaceutical and clinical reviews. Regarding the validity of the findings from the abandoned trials, we made sure that there were no ethical concerns regarding their methods and that the extracted trials were randomized and controlled trials that did not suffer from faulty design. We searched academic databases like PubMed, National Library of Medicine and Google Scholar using keywords such as "drug effects," "brain development," and "age comparison." We focused on studies published within the last 10 years and included both experimental and observational research. To ensure quality, we only selected peer-reviewed articles and assessed them using standard evaluation criteria; we made sure to consider the credibility of the author for each paper we utilized, considered the purpose of each article and their intended audience, and we also ensured accuracy and dependability of the research we utilized by comparing their findings to repeated trials (if available) or other similar research data and conclusions. We then carefully read each study, extracting key information about methods, findings, and conclusions regarding both adult and children patient groups by searching for keywords such as "adverse/intended effects," "brain," "response". Finally, we organized this information into themes (patient age groups, intended effects, pharmacodynamics, and adverse effects), comparing

and contrasting the effects of various drug classes on children's and adults' brains.

Throughout the process, we were mindful of potential biases such as selective presentation of data that would overlook major disadvantages or advantages of a certain drug; thus, aimed to present a balanced view of the current scientific understanding on this topic.

Results

For both children and adults, a multimodal treatment approach with psychotherapy is found to be the recommended line of response. Although medication is prescribed in many cases, it is not the only line of defense in battling anxiety disorders. There are many other forms of treatment that often take place before prescription of medication: exposure-based cognitive behavioral therapy, family therapy, and patient and family education. Additionally, it is only because the safety and efficacy of drugs other than selective serotonin reuptake inhibitors (SSRIs) has not been completely established that SSRIs tend to be the recommended choice of medication and are used much more than other classes of medications .

SSRIs work by "inhibiting" the reuptake of serotonin, which is a neurotransmitter in our brains that is usually reabsorbed by nerve cells. This reabsorption is known as reuptake. Although individual responses to medication can vary significantly due to factors such as genetics, metabolism, and underlying comorbidities, the pharmacokinetics of SSRIs are identical for both children and adults, as the drugs are absorbed, distributed, metabolized, and excreted the same way. There are, however, slight differences in the metabolism due to children and children having a faster metabolism; dosing of SSRI that are typically given once a day for adults might need to be divided into twice a day doses to prevent withdrawal effects. When SSRIs are successful in facilitating the neural responses that they are intended for, there seems to be very little variation in responses between that of adults and children. However, when considering the possible side effects of SSRIs, there are clear differences between children and adults regarding what side effects are possible or common. There still exists similarities in side effects for both groups, classified as "common side effects" such as gastrointestinal disturbances including but not limited to nausea, vomiting, diarrhea, flatulence, and decreased appetite. Gastrointestinal side effects occur as a result of mediated stimulation of serotonin 3 and 4 receptors by SSRIs, which cause symptoms like nausea and vomiting; the intended receptors that SSRIs are supposed to target are 5-HT receptors.

Additionally, sleep disturbance is another side effect occurring for both adults and children. Disturbances in sleep patterns occur as a result of the activated serotonin receptors, which can suppress REM sleep. Sleep disturbances often occur during the first few intakes of SSRIs and are a temporary side effect that will resolve itself over the course of a few weeks.

While adults and children both share the common side effects of SSRIs, some side effects are found to be increased in intensity. For example, serotonin syndrome (SS) is a side effect of SSRIs that occurs when serotonin levels reach unusually high levels in one's brain, causing confusion, agitation, muscle twitching, sweating, shivering, and diarrhea. This condition is usually triggered when a patient is taking an SSRI in combination with another medication that increases serotonin levels. SS appears to be more common in pediatric patients than in adult patients; although a definite reason isn't available, it is assumed that because children's brains are still developing, they are more susceptible to SS since their threshold for "too much serotonin" are almost guaranteed to change as they experience growth and bodily changes; natural changes in the human body as children mature also facilitate changes in hormone and neurotransmitter levels.

Similarly, children with anxiety disorders are more likely to experience withdrawal syndrome due to the differences that occur as a result of ongoing brain developments for children. This side effect can present itself in the form of gastrointestinal disturbances within 2-5 days of reduced dose or discontinuation and are mostly resolved within 1-2 weeks. However, the intensity of the withdrawal effects varies depending on the specific SSRI and the duration of its use. Additionally, another major difference in side effects between children and adults is behavioral activation within patients. Especially more common within children's due to their developing brains (20%-50%), behavioral activations present themselves through alterations in mood, dysphoria, and mania (these symptoms are not indicative of bipolar disorder). Also, while not specific to SSRIs, all antidepressants including SSRIs have been issued a warning by the FDA in 2004 regarding the risk of suicide ideation among children; their analysis was taken from 24 trials of 9 antidepressants (including SSRI) in over 4,400 patients[6]. The test revealed the increased risk of suicide among children and children being treated with antidepressants and recommended close monitoring of these pediatric patients, especially during the first few days.

Although SSRIs are considered to be the first line of psychopharmacological intervention for both adult and pediatric patients, differences are still present in regards to the side effects and the degree of severity the patients might experience[7].

Benzodiazepines (BDZs) increase the binding of gamma aminobutyric acid (GABA) by acting upon benzodiazepine receptors in the CNS. The receptor, namely the gamma-aminobutyric acid type A (GABA-A) receptor, is composed of 5 transmembrane subunits that collectively form a chloride channel in the center. The subunits are 2 alpha subunits, 2 beta subunits, and 1 gamma subunit. The extracellular portions of the alpha and beta subunits form a receptor site for GABA, a neurotransmitter that slows down brain activity. The extracellular

portions of the alpha and gamma subunits form a binding site for benzodiazepines. This binding opens up the chloride ion channels, resulting in hyperpolarization of the cells and greater entry of chloride ions. This influx of chloride ions induces feelings of calm, drowsiness, and sleep.

Additionally, Benzodiazepines are classified as class IV-controlled substances within the U.S. Tolerance. There are a total of 5 different classes (Schedule I through Schedule V), with I being the most dangerous due to their potential to induce severe psychological or physical dependence, and V being the least dangerous [8]. Despite its classification as class IV, the risk for abuse of or dependence on benzodiazepine is still present for both pediatric and adult patients, especially with higher doses and long-term uses of BDZ.

Regardless of a patient's age, BDZs are rarely chosen as first-line treatments for anxiety disorders due to their potential to cause harm. They are more often recommended for short-term use or for treating procedural anxiety rather than for long-term treatment of anxiety disorders. In a PubMed study, 21 trials involving 1,416 patients assessed the efficacy of benzodiazepines as short-term anxiolytics in pediatric patients through a fixed effects model [9]. Their results indicated that BDZs were effective and well-tolerated when used as short-term anxiolytics in procedural settings for pediatric patients, but efficacy in pediatric anxiety disorders remained unclear. Akin to a handful of other anxiety disorder medications, the pharmacokinetics of BDZs remain identical in both children and adults and will produce similar responses in both groups when the GABA-A receptors are activated properly. While most differences in drug responses between children and adults often reveal themselves through the increased risk or emergence of an entirely new side effect for pediatric patients, this does not seem to be the case for BDZs.

Common side effects of BDZs present themselves through sedation, cognitive blunting, dizziness, memory impairment, ataxia (neurological sign that indicates lack of muscle coordination), and nystagmus (condition causing involuntary, rhythmic, rapid or slow eye movements) that develop as a result of the influx of chloride ions through the GABA-A receptor, which slows down the CNS by hindering the firing of action potentials in neurons. When BDZs are abused, taken in larger doses than recommended, or absorbed in combination with other depressants, BDZs can produce adverse side effects such as depression, transitory hallucinations, and delusions [10]. Due to the sense of euphoria and pleasure that BDZs induce in patients, many people abuse their prescription of BDZs, depicting the increased risk of abuse and dependence with higher dosages and long term uses; for both children and adults alike, BDZs should be tapered when discontinued to prevent withdrawal symptoms from emerging. Similar to SSRIs, these withdrawal effects depend on the specific BDZs and the duration of their use. These side effects are common in both children and adults at similar rates, suggesting that, at least for benzodiazepines, there are no noticeable differences in responses between children and adults.

However, there is one adverse effect of BDZs that pediatric patients are at increased risk for: paradoxical reaction (a reaction to a drug that is the opposite of the expected effect)6. Characterized by behavioral disinhibition, loss of control, increased anxiety/aggressiveness, rage reaction, and nightmares or hallucinations, paradoxical reactions are a significant concern for pediatric patients who have not yet developed the skills to control their behavior in adverse situations. As of now, the neurobiology of the paradoxical remains unclear, but it is known that risk factors for developing a paradoxical reaction from benzodiazepine include alcoholism, extremes of age (children or elderly), and psychiatric cormobidity [11]. Additionally, elderly patients are at increased risk of falls and cognitive impairment from the slowed-down CNS caused by the binding of BDZs to GABA-A receptors. Benzodiazepines, although not recommended as the first line of medication against anxiety disorders, have very little variability in responses when comparing pediatric patients and adult patients.

Buspirone is another class of medication that acts as a partial agonist at 5-HT1A receptors, which can modulate both serotonergic and dopaminergic activity. They suppress serotonergic activity while enhancing dopaminergic and noradrenergic cell firing. This class of medication disproves the notion that only one neurotransmitter mediates anxiety disorders. Buspirones have a high affinity for 5-HT1A and 5-HT2 serotonin receptors, and is a partial agonist that ameliorates symptoms of anxiety through its postsynaptic partial agonist actions [12]. Rapidly absorbed after oral ingestions for both children and adults, buspirone reaches peak plasma levels (highest concentration of drug in the bloodstream after administration) between 40 to 90 minutes after oral dose. Unlike some other anxiety medications, buspirone doesn't display full effect right away, taking anywhere between 2 to 4 weeks before it reaches its full effect for pediatric and adult patients alike. Although buspirone have not been FDA approved in children, a 2018 study utilized prospective, randomized, parallel-group controlled trials of buspirone in pediatric patients with GAD, as well as data of associated pharmacokinetic studies to indicate that buspirone is generally well tolerated in pediatric patients with anxiety disorders, displays similar side effects to those seen in adults, and discontinuation is same as SSRI and SNRI [13]. The fact remains, however, that this medication's lack of approval from the FDA nods at how it is not a reliable treatment for children with anxiety.

For both children and adults, buspirone is often used as an adjunctive agent along with SSRIs to assist patients who don't respond to standard antidepressant therapies (buspirone also alleviates sexual dysfunction associated with SSRIs). Although considered rare cases for both pediatric and adult patients, serious side effects of buspirone include allergic reactions and serotonin syndrome; however, buspirone hardly displays such serious adverse effects, and therefore are often used as initial drugs when

treating anxiety disorders[14]. Most side effects are generally mild for children and adults alike, including headaches, dizziness, nervousness, drowsiness, nausea, weakness, blurred vision, and excitement due to the serotonin modulation and dopamine interaction caused by buspirone. No specific side effects are particularly concerning for pediatric patients. Additionally, this class of medication is not associated with physical or psychological dependence, meaning no significant withdrawal symptoms will occur when discontinued[5].

Discussion

Anxiety disorders, like many other mental conditions, have a number of methods of treatment apart from medications such as continued CBT, which has proven to be highly effective in decreasing anxiety symptoms and improving functioning for children with anxiety disorder. Nonetheless, pharmacological methods are still thought to be the first line of response. The classes of medication mentioned in this paper are just 3 of many more that can be used either alone or in conjunction with another class in ameliorating anxiety disorders and their symptoms. The comparisons made in this paper provide different and nuanced answers for each class of medication regarding the presence of differences between children and adult responses. Despite possibilities of differences in medication effects due to confounding factors, the pharmacokinetics remain the same for all 3 classes (SSRIs, Benzodiazepines, Buspirones) for both pediatric and adult patients; any differences found in their responses cannot be attributed to differences in methods of absorption or metabolism of the medication.

SSRIs generally produce the same responses in both groups when the medication is successful in producing the desired responses. However, differences emerge when the drugs produce side effects; adverse effects of SSRIs tend to be increased in intensity within children. But it would be an oversimplification to state that all children experience increased susceptibility to side effects as individual responses can vary widely; our study results are only pointing at the general trend that seems to emerge among children. Such side effects include serotonin syndrome, withdrawal syndrome, behavioral activation, and suicide ideation. A definite reason for increased risk of these effects on children is not yet available, but it is implied by many studies that because the children's brains are constantly undergoing change as they age and continue to develop, so do the threshold and production of chemicals in their brains. For example, serotonin syndrome occurs as a result of the brain producing "too much serotonin." For children, whose developing nervous systems are more sensitive to such serotonin producing medications, their threshold for serotonin syndrome could be lowered; in fully developed brains (person over age of 25), serotonin processing and receptor sensitivity are stable at this point, which reduces the risk of serotonin syndrome (more likely to be influenced by changes in dosage or interactions with another drug). Brain development alone most likely isn't the only factor that contributes to intensified side effects for pediatric patients taking SSRIs, but age-related factors such as drug metabolism and receptor sensitivity variations most likely play a role in increasing the risk of adverse effects at different stages of life. This interpretation also implies that increased risk isn't just present in children and children; older adults experiencing age-related decreased kidney or liver functions that impair drug metabolism are also more susceptible to serotonin syndrome from SSRIs.

Serotonin is not the only neurotransmitter that influences anxiety disorder symptoms; another class of medication, namely benzodiazepines, alleviates anxiety by opening up GABA-A receptors that allows an influx of chloride ions to pass through, inducing calmness. This class of medication, similar to SSRIs, generally has no difference between children and adults in terms of "desired effect" responses, as the intended effects are the same for both pediatric and adult patients. The few differences that arise from these two groups are present in the side effects of this drug as well. For BDZs, however, there are fewer variations in susceptibility to side effects between pediatric and adult patients when compared with SSRIs. BDZs have only one side effect where pediatric patients are at increased risk: paradoxical reaction. Although the exact neurobiological pathway for this reaction is unknown, reasons for paradoxical reactions include doses being too high or too low for individuals, possessing tolerance to the drug, variations in metabolisms, or influence of brain chemistry. The increased risk of paradoxical reactions from benzodiazepines for children and the elderly emerge most likely from their developing nervous systems, which might produce unexpected responses, differences in drug metabolisms, which can alter drug levels in the body, or the inability to control their behaviors during these reactions. Children's brains, especially in areas related to neurotransmitter regulation (including the GABA system), are not fully developed, and this incomplete brain can produce unusual responses such as paradoxical reactions. Additionally, children's liver enzymes do not function the same as adults, meaning that children metabolize drugs differently than adults (hence the difference in doses for children compared to adults). This difference in the ability to metabolize most likely contributes to unusual side effects such as paradoxical reactions. Once again, this reference to drug metabolism as a factor for varying susceptibility to side effects indicates that elderly people are also at increased risk for such adverse effects.

Yet another class of medication that is used to treat anxiety disorders is buspirone. Buspirones influence 2 neurotransmitters, dopamine and serotonin, solidifying the notion that anxiety disorder symptoms are influenced by more than one neurotransmitter. While buspirone have not been FDA approved for children, a 2018 study displays not only its effectiveness in treating anxiety disorders, but also its low variability in responses between adults and children13; the side effects of buspirone are generally

mild and similar for both pediatric and adult patients, indicating that responses are predictable for both groups without any one group having intensified symptoms or increased susceptibility. Having the same discontinuation as SSRI and SNRI, buspirone is oftentimes used to support SSRIs. In other words, buspirone does not display any differences in response between pediatric and adult patients. However, the use of buspirone as a reliable treatment for children with anxiety requires further investigation to establish its efficacy and safety profile in this population. For each class of medication, the variability in response between adults and children differ. SSRIs displayed a noticeable difference in the symptoms and susceptibility of their side effects, BDZs displayed little variability, and buspirone displayed no variability at all. These results suggest that for predictability, buspirone is the best, but this is not the case; SSRIs are still the recommended first line of medication for alleviating anxiety disorder symptoms and neither BDZs nor buspirone have been FDA approved for children. While SSRIs are considered the most effective medication in treating anxiety disorders, the lack of predictability in responses from children indicate that further research is required in order to stabilize the variability it displays within pediatric patients.

The limitations of this study mostly stems from its reliance on existing research and potential bias. All data originated from previous work done by other researchers and has not been individually confirmed for the purpose of this study; this study combines results and findings of various research to synthesize another set of data and findings that answer a different question. Additionally, the potential bias within this study is not to be overlooked, as it could've influenced the interpretations of the findings and the implications that were more highlighted than others. The scarce availability of statistical evidence in the clinical trials and research that were extracted for data proved to be another limitation of this study as the qualitative statements were often not backed up with quantitative evidence.

However, this study concludes that although certain types of drugs are yet to be studied to this extent, the data available for the drugs that have been studied and their implications provide deeper insight as to how we can address the biological and structural differences between children and adults when developing medications or treatment methods for mental disorders. This comparison reveals that, at least for psychiatric medications, age differences prompt different susceptibility and intensity for side effects of certain classes of medication. Additionally, our findings contribute to the question of how side effects can be reduced for drugs by adding a follow up question: How differently, if at all, should side effects in pediatric patients be addressed compared to side effects in adults? If differences in drug metabolism and developments in the nervous system are assumed to influence their susceptibility to and intensity of side effects, it indicates that these differences must also be accounted for when developing methods to reduce or minimize these side effects. Further investigations will need to be conducted in order to fully dissect and understand the roots of these differences. Because the presence of these variability can largely be attributed to the different age groups across our population, it is important to consider these factors when prescribing anxiety medications.

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