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The Effects of Psychotropic Medications on Developing Brains

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Abstract

Diagnoses of mental illness among children and young adults are pervasive in our communities here in the United States. And the early onset of these mental disorders in children has been linked with devastating effects that are not just limited to self-injurious behaviors, suicidal ideations or attempts, drug and alcohol abuse, school truancy and interpersonal conflicts. Of course different treatment modalities are applied to mitigate and address these conditions, however, psychotropic medications are among the leading, if not the leading treatment tool in dealing with these psychiatric and behavioral diagnoses among children of all ages. However, treatment challenges often and unfortunately carry increased rates of complications for young children including the unborn children exposed to these drugs. This paper seeks to highlight from current and trending studies, the implication of psychotropic medications on the brains of children and adolescents; do they have long-term adverse effects on the developing brains of these children? Do the benefits outweigh the risks? Is there a better alternative or hope for a better alternative in the future?

Effects of Antipsychotics on the Development of Children's Brains and Behaviors

More and more children as young as age 6, and in some cases even younger are increasingly being prescribed psychotropic medications like never before. The pervasiveness of Attention Deficit Hyperactive Disorder (ADHD) with other behavioral dyscontrol among children have led to a massive prescription by both psychiatric and medical providers of ADHD and psychotropic medications for children. Many other children are exposed to antipsychotics in-utero from women who used antipsychotics while pregnant, a trend that does not seem to be declining but rather increasing with time.

Clinical Case Report

During my clinical rotation with the children and adolescents, there were many children most of who are between the ages of 6 and 12 that have the same or similar diagnoses, some of which includes but not limited to Generalized Anxiety Disorder (GAD), Attention Deficit Hyperactive Disorder (ADHD), Major Depressive Disorder (MDD), Oppositional Defiant Disorder (ODD), Adjustment Disorder (AD), Autism Spectrum Disorder (ASD) insomnia and Parent Child Conflict (PCC). From personal observation, it is noted that the younger the child or a male gender, the higher a likelihood to have a diagnosis of ADHD, and the older adolescent females are mostly diagnosed with GAD, PCC, ODD or MDD. Major psychiatric disorders common among adult patients such as schizophrenia, bipolar, Obsessive Compulsive Disorder (OCD) and delusions are very infrequent if not totally absent.

A case in point that called my attention even further to this issue is from a 12-year old female patient with diagnoses of Depression, GAD, Mixed Obsessional Thoughts, nightmares, OD, and PCC. She has a significant history of running away from home, refusing to take her meds, truancy from school, physical aggression towards her mother and self-injurious behaviors. Her

parents are divorced and she's living with her mother and her mother's boyfriend, but also stays with her father during school breaks or some weekends. During their appointment all members of the family were present including her mother's boyfriend, and from their account she gets along better with the 'fathers' than the mother. Her biological father stated that she never threatens him or herself during their times together and thinks that her mother is trying to make the child thinks and acts like herself, a statement that led to a verbal altercation between the two of them.

Her problems leading to these diagnoses started shortly after her parents' divorce and has been prescribed Sertraline 100 mg daily and with Vistaril 25 mg as needed since, which were ineffective because she has been non-compliant and running away from home. Her needs included a higher level of care placement including a referral to see a personal therapist.

This case is not mutually exclusive to other cases noted in this clinical rotation, and all of which are complicated in their respective ways. However, my observation made me believe that the issues has more to do with just the children's behavioral dyscontrol or psychiatric condition; most of these behaviors and disorders do not start overnight. Family history, social or environmental, and especially living conditions at home are all contributing factors thus therapy and multi-disciplinary treatment modalities should be the foremost approach. I think medication-alone approach would yield unintended negative consequences for these immature minds.

Literature Review

Studies indicate rising frequencies of antipsychotic medication use with concurrent use of polypharmacy among children overall, and in children with autism spectrum disorders (ASD). And the common worries about these medications include the lack of proof supporting the safety and/or efficacy of psychotropic treatment in children, when developing brains and bodies may be especially susceptible to environmental and/or biological impacts (Spencer et al., 2013). They

further indicated that the only medications approved for the treatment of ASD are risperidone and aripiprazole to treat irritability and aggression respectively. Nevertheless, providers often prescribed these medications in an off-label, trial-and-error manner for children to help control problematic symptoms, particularly if there are no other treatment options. There is even less knowledge about the safety and efficiency of antipsychotic polypharmacy and possible interactions between medications that could affect children with complicated psychiatric disorders, such as ASD. Therefore, detailing psychotropic use and polypharmacy among children with ASD is fundamental for informing families, providers and academics.

Spencer et al., (2013) posited that from a study of 33, 565 children with ASD, it was found that 64% of them used at least one antipsychotic medication, and about 35% had evidence of psychotropic polypharmacy during an average length of enrollment greater than 3 years. About 15% of them had psychotropic polypharmacy that included at least 3 classes of medications, commonly used of which were antidepressants and Attention Deficit Disorder (ADD) medications, psychotropic medications and ADD medications, psychotropic medications and antidepressants, and the all 3 of antipsychotics, antidepressants and ADD medications. In these, those children with indication of polypharmacy received the treatments for a longer period than those without.

Although current evidence for the efficacy of polypharmacy treatment of children with ASD has been described as inadequate, psychotropic medications are frequently used for ASD and its co-occurring diagnoses. Further study is needed to know why they are being used and whether present practices are as result of trial-and-error in children or if there is a more systematic awareness of need and benefit. Safety issues are worrying since many of these medications have already shown safety concerns when used by themselves with even higher possibility for toxicity when they are combined. A way forward using claims data would be to connect medication use

with symptoms and diagnostic suggestions, and as well as monitor both short and long-term results just like adverse effects, medication changes, acute care visits, and overall health and morbidity outcomes. Furthermore, knowledge about the scientific developments in the utilization of psychotropic medications is contained within claims data and remains uncharted. Lastly, claims-linked patient registries may hold promise for knowing the different needs and outcomes of diversified children with ASD (Spencer et al., 2013)

Pointing out the role of prolactin and dopamine on the developing fetal brain, Yarlagadda et al., (2015), states that clinical depression occurs in more than 10% of women during pregnancy, while postpartum depression occurs between 10 to 22% of women. For those women diagnosed with moderate to severe depression, psychotropic medications could help both mother and infant during pregnancy and the postnatal period. The use of antipsychotic medications during and after pregnancy has been debated for many years, because they can be conveyed to the fetus through the placenta and through breast milk to the baby. Nevertheless, most antipsychotic medications are termed reasonably safe for children during lactation.

What warrants assessment is the possible connection between the prolactin dopamine ratio exposure in utero and the growth of developmental disorders in children. Placental impediment exists for pervasive developmental disorders (PDD), such as the one explained by Holmes et al for stress hormone effect on fetal mice brain. They presented evidence in mice of fetal growth decrease together with growth of mood disorders later in life thus supporting the theory that placental 11-beta-HSD2 is a crucial impediment to maternal glucocorticoids. Another review research produced credible proof for multiple interacting genetic features as the sole contributing determinants of autism. They also revealed that data from whole-genome screens in multiplex families indicate interactions of at least 10 genes in the causation of autism. In a study of the

allelic associations between genetic variants in six genes (oxytocin [OXT], oxytocin receptor gene [OXTR], prolactin [PRL], prolactin ligand receptor [PRLR], dopamine beta hydroxylase [DbH, and Finkel-Biskis-Jinkins (FBJ) murine osteosarcoma viral oncogene homolog B (FosB) it's observed that these are involved in the control of maternal and affiliative behaviors. They denoted a relationship between the PRL ligand and the prolactin receptor that have allelic associations with ASD, which may show the direct involvement of the PRL pathway and probable indirect effects of other pathways with which PRL interacts. The study also noted an allelic connection between ASD and the OXTR (Yarlagadda et al., 2015).

Over the past 20 years, the use of more than one psychotropic medication in children has become increasingly common. Combining psychotropic medications may have some benefits but also comes with risks, especially by looking at the possible adverse effects from drug interactions. Yet there is very limited evidence from controlled clinical studies to help prescribers do their work efficiently, despite the growing use of psychotropic medication therapy in children and adolescents. Because of this therefore, the practice and guidance are running ahead of the science (Jureidini, Tonkin & Jureidini, 2013). They further posited that through a narrative review, the available evidence for efficacy and safety for combining use of psychotropic medications in children is small. Jureidini, Tonkin and Jureidini, (2013) also stated that from a comprehensive 37 research studies published, of which 18 were randomized controlled trials (RCTs) focusing mainly on stimulants, central sympatholytics, example clonidine, antipsychotics and mood stabilizers. Very small percentage of it showed significant merits for dual pharmacotherapy over monotherapy, and adding central sympatholytics to stimulants for treating ADHD symptoms was supported by extensive studies with an effect size large enough to suggest clinical importance. From this non-randomized studies seem to have results that favors concomitant treatment, but all have design-

related issues thus decreasing the reliability of the outcomes. Other studies that individually research tolerability of combination pharmacotherapy in relation to monotherapy, indicated stark increases in adverse effects including sedation and self-harm, both subjective and objective. They concluded that by given the ambiguity of evidence for benefit with potential evidence for harm, therefore, further study needs to be done as a matter of urgency. And until then, the approach to combination pharmacotherapy should be moderate, and combining psychotropic drugs should be carefully checked for use in children (Jureidini, Tonkin & Jureidini, 2013).

A developing brain is reliant on the occurrence of critical developmental processes such as synaptogenesis and thus sensitive to medication interventions. Treatment with serotonergic (5-HTergic) or dopaminergic (DAergic) medications like fluoxetine (FLX) and methylphenidate (MPH), is hence likely to have influence on the maturation of the brain. For the 5-HTergic systems, FLX, known for the treatment of depression in children is found to increase extracellular levels of 5-HT by blocking the serotonin transporter (SERT). Conversely, animal researches have shown that preadolescent 5-HT pharmacological manipulations can lead to atypical outgrowth of the 5-HT system. Studies have indicated that long-term treatment with FLX results in a significant increase in prefrontal and hypothalamic 5-HT transporter in juvenile-treated rats, but not in adult treated rats; findings that are in tandem with Wegerer and Bock who have also stated that this effect continues into adulthood even long after the treatment with SSRIs has stopped. It was recently confirmed that FLX administration up-regulates SERT long-lastingly, also in non-human primates. These preclinical studies suggest that 5HTmanipulations have an effect on the regulation of 5HT extension that is reliant on the age of exposure (Bottelier et al., 2014).

By looking at some of the reasons why there have been increasing influx of more young children taking psychotropic drugs today, and more specifically stimulants and antidepressants; the

utilization of some stimulants in 2 to 4 year olds has escalated to an average of 260% across 3 places between 1991 and 1995. This led to a momentum of investigations of medication prevalence in young children starting from the White House, the National Institute of Health (NIH), with other professional bodies (Fritz, 2000).

Given the particular risks and doubts associated with psychopharmacologic treatment in young children, what reasons might be behind the increased use of such psychotropic medications? One probability is scientific interest; as more is understood about the human genome, it's becoming clear that most psychiatric disorders have a substantial genetic element and that the risk for adult disorder hypothetically, is known early in childhood. However, environmental changes can change the expression of a gene thus successfully altering the risk for adult disorder. This knowledge leads mental health professions toward earlier mediation in order to prevent severe psychopathology later in life, and medications represent one viable physiologic intervention. Also, and though less commendable possibilities that in a time when monetary concerns command treatment, medication prescription requires less time than other treatment options, thus is cheaper, a fact not lost on those who pay for their own treatment. Most providers have experienced managed care reviewers' not-so-subtle expectations that serious treatment involves medications. Also, the millions of dollars focused on physicians may very well influence their prescribing practices and force from parents or teachers for a medical answer to young children's behavior problems that have intricate causes. Whatever the reasons, we need to take a serious look at whether society’s desire for quick, inexpensive solutions is coming at the cost of inappropriate medication use in children (Fritz, 2000).

According to Bronson (2002), 5 million children are prescribed psychotropic medications and for those under the age 6, the usage has increased up to 580%, for ages 7 to 12 it went up 151%

and these drugs include stimulants such as Adderall, Ritalin and Concerta. Drugs that are worrying in their neurochemical implications and many of these children stay on them for long periods of time with reports from parents that these symptoms are not getting any better. A biochemical assumption that might be responsible for this is that there is an intricate interaction between the neuronal growth of children and adolescents, which is the place of logic and reasoning. And it is not until the age of 25 for boys and about 23 for girls to have their prefrontal cortex to fully grow. Thus the exposure of these underdeveloped brains to xenobiotic chemicals affects the plasticity of the brain. When children who are susceptible to dopaminergic excess combined with the underdeveloped prefrontal cortex, you'll have an emotionally labile child who would go from anger to revenge without a transitional process of logic and reasoning. They will lack good judgment if they don't have the neuronal capacity to do so.

There have also been reports of increased rates of heart anomalies in the children of mothers who used SSRIs during pregnancy supported by animal research that have pointed to serotonin as the target of many antidepressants, in the development of the brain and other organs. Serotonin is expressed in the brain early in prenatal development that could change dendritic and axonal differentiation, and early postnatal interruption of serotonin signaling in animals have shown to constantly increase anxiety with learning disability (Thompson, Levitt, & Stanwood, 2009).

Teaching children how to expect breakdowns in life is what needs to be emphasized first and foremost. Breakdowns is an ability that the growing brain has to learn; many of the children who express risky behavior have an inclination to dopaminergic excess, an affinity to dopaminergic chemicals like cocaine, thus they do things like hunting for that adrenaline rush (Bronson, 2002).

Following approvals of the joint panels founded to assess the risk of suicidality for youths taking antidepressants, the FDA instructed drug manufacturers to amend their labels to include a black box warning to alert providers and consumers that antidepressants increase the risk of suicidality in children with depression hence can contribute to clinical worsening and unusual changes in behavior. Despite this advice, the use of psychotropic drugs in children continued to increase because many family clinicians often do not have the time or expertise to sift through drug studies and to engage in informed critical analysis. They may not know that other major drug tests of SSRIs for children suffer from similar design problems, including inactive placebos and inadequate lengths of time. They may also be unaware of the true extent of industry influence on research and the dissemination of research as advertisement into the general public (Sparks & Duncan, 2008).

Many drugs that are prescribed by psychiatric clinicians such as antiepileptic are also among the most common teratogenic (causing birth defects) drugs being prescribed to pregnant women. Drugs, which are found to be linked to both anatomical and cognitive or behavioral malformations. There are other antiepileptic drugs such as lamotrigine and levetiracetam that appear to show low risks for both anatomical and behavioral anomaly. Nevertheless, the knowledge of their teratogenic risks and underlying mechanisms remains insufficient and also its long-term consequences in children remain ambiguous (Meador & Loring, 2015).

There cannot be a total lack of benefits for children using psychotropic medication however; studies also indicated that children with ADHD have increased risks of injuries compared to children without it. And treatments with stimulants such as amphetamine and methylphenidate have proven to reduce the risk of injuries by up to 43 percent and emergency (ER) visits by up to 45 percent. These results are imperative public health concerns since accidents are the most

common cause of death among children with ADHD (Dalsgaard, Leckman, Mortensen, Nielsen & Simonsen, 2015).

Conclusion

Sparks and Duncan (2008) posited that lack of awareness takes on greater risks where children are concerned; they trust providers to know and to make good decisions on their behalf, thus an ethical approach demands that clinicians become aware of the association between a profit-driven industry and science. Becoming knowledgeable through critical analysis enables providers to help clients to look beyond the ads and brochures in making decisions about their child's course of treatment. Only then can an accurate risk or benefit analysis be undertaken. In absence of a rational skepticism and active critique, providers, even with the best intentions, are complicit in a for-profit enterprise where client interests take a back seat.

Providers need to conduct a thorough and systematic assessment of the child's problem, seeking information from the family, school, and other involved parties. Develop a conjoint background for understanding the problem based on the youth, family and interactional explanations. Develop a plan that follows the assessment and background of understanding. If medication is part of the plan, help the family to view positive change as resulting from the efforts of all, in overcoming the problem, and include discussion of a time frame for discontinuation of medication (Sparks & Duncan, 2008).

Researchers and academics often find it confusing that what seem to be rudimentary concepts of development are misconstrued by law makers, therefore establishing policies that are not evidenced based to guide appropriate development. Creating simple developmental strategies that will unambiguously communicate these influences will be vital in assisting law makers to enact better strategies for decreasing the occurrence of drug exposure to children during and after

pregnancy, and to device more efficient treatments that would optimize healthy development even if drug exposure has to happen.

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