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PERSPECTIVE

Sterol biosynthesis disruption by common prescription medications: critical implications for neural development and brain health

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Sterol biosynthesis is essential for cellular function, producing not only cholesterol but also critical bioactive molecules that regulate cell signaling, growth, and membrane function. In the brain, cholesterol metabolism operates independently behind the blood–brain barrier, maintaining its own homeostatic balance. An emerging concern in clinical pharmacology is the discovery that many common prescription drugs unintentionally interfere with post-lanosterol sterol synthesis pathways. While acute effects of these medications are documented, their long-term consequences for brain development and function remain unclear. Studies using cell cultures and mouse models indicate heightened risk during pregnancy, where drug-induced sterol disruption may interact with genetic factors from both mother and fetus, particularly when multiple medications are prescribed. This significant research gap has important implications for clinical practice. Our review consolidates current evidence about how prescription medications affect post-lanosterol biosynthesis and outlines critical areas requiring urgent investigation.

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Introduction: Brain Sterol Biosynthesis is Critical for Normal Brain Development and Function

Cholesterol is essential for all mammalian cells, especially brain cells (1). The human brain accounts for approximately 2% of total body weight, yet it contains about 25% of cholesterol and cholesterol derivatives of the human body (2–4). The body's and the central nervous system (CNS) cholesterol pools are separated by the blood–brain barrier (BBB), each relying independently on its intrinsic cholesterol biosynthesis (5). Brain sterol biosynthesis starts during intrauterine development and continues throughout the patient's lifetime (5, 6). In an unesterified form, brain cholesterol is predominantly found in the myelin sheaths and plasma membranes of the various brain cells (2, 6).

Synapse and dendrite formation and axonal guidance are both sterol-dependent processes, and the sterol biosynthesis pathway generates dozens of bioactive molecules critical for normal brain function (7–11). Preserved cholesterol homeostasis is also necessary for regular functioning of the adult brain: in aging, high brain cholesterol has been connected to better memory function, while low cholesterol is associated with an increased risk for depression (12–14). In addition, disturbances in cholesterol biosynthesis and/or metabolism have been reported in Huntington's disease and Alzheimer's disease (15–17). Low cholesterol concentrations may predispose an individual to aggression, impulsivity, and violence (18–20).

Cholesterol Biosynthesis is a Complex Biochemical Process

Cholesterol is synthesized from acetyl-CoA in a long cascade of two final parallel chains of enzymatic events called the Kandutsch-Russell and Bloch pathways (Figure 1) (21). Conversion of the final sterol precursor, 7-dehydrocholesterol (7-DHC), to cholesterol is mediated by DHCR7 in the Kandutsch-Russell pathway (22). In the Bloch pathway, DHCR7 is necessary for the reduction of 7-dehydrodesmosterol (7-DHD) to desmosterol (DES) (23). Thus, disruption of DHCR7 function prevents normal cholesterol production through both post-lanosterol biosynthetic pathways and results in elevation of 7-DHC and 7-DHD and reduction in cholesterol and desmosterol levels (24).

7-DHC and 7-DHC–Derived Oxysterols have Strong Biological Effects

Reduced cholesterol production is detrimental to the brain, but the arising pathophysiology is more complex (25). As cholesterol precursors 7-DHC, 8-DHC, and 7-DHD accumulate (24, 26, 27), a new challenge emerges: 7-DHC is the most oxidizable lipid known to date, with a propagation rate constant of 2,160 (this is 200 times more than cholesterol and 10 times more than arachidonic acid) (28, 29). As a result, 7-DHC spontaneously oxidizes, generating highly reactive 7-DHC–derived oxysterols (30), impairing cell viability, differentiation, and growth (31, 32). The most investigated 7-DHC–derived oxysterol, DHCEO, interferes with neuronal morphology, neurite outgrowth, and fasciculation (31, 33). Furthermore, 7-DHC–derived oxysterols are simultaneously markers of oxidative stress (34) and biologically active molecules that modify immune function (33, 35). 7-DHD and 8-DHC, while much less studied, are also likely to generate their own oxysterols, as they have a comparable peroxidation rate to 7-DHC (29).

Pathogenic Variants in Sterol Biosynthesis Genes Result in Developmental Disabilities

While a complete lack of cholesterol biosynthesis is incompatible with life, partial cholesterol production due to pathogenic variants in post-lanosterol genes results in complex developmental disabilities (36). Mutations in post-lanosterol biosynthesis are associated with Smith-Lemli-Opitz syndrome (SLOS) (mutations in DHCR7) (25), desmosterolosis (mutations in DHCR24) (37, 38), chondrodysplasia punctata 1 [mutations in emopamil binding protein (EBP)] (39, 40), and lathosterolosis (mutations in SC5D) (41). All these syndromes affect brain and craniofacial development and lead to intellectual and developmental disabilities (36, 42).

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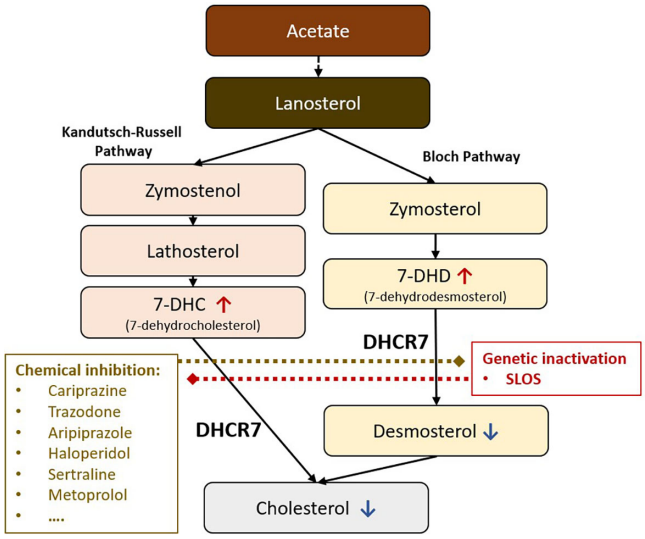

Figure 1. Commonly used prescription medications have a post-lanosterol biosynthesis inhibiting effect. Pathogenic variants in the DHCR7 gene result in SLOS with a hallmark sterol inhibition signature. This profile encompasses the accumulation of 7-DHC and 7-DHD and the reduction of desmosterol and cholesterol levels. Many commonly used prescription medications give rise to similar biochemical signatures and can be considered sterol biosynthesis inhibitors. The post-lanosterol pathway is greatly simplified for readability.

DHCR7 Inhibitors During Pregnancy are Considered Teratogens

Boland and Tatonetti published a systematic literature review in 2016, which revealed that first-trimester exposure to DHCR7 inhibitors met the criteria for teratogenicity. As a result, they suggested that DHCR7 activity should be considered during drug development and prenatal toxicity assessment (43).

Many Prescription Medications have Sterol Biosynthesis Inhibiting Side Effects

While cholesterol and post-lanosterol intermediates do not cross the BBB, many prescription medications do so easily (44). These medications, designed for unrelated primary indications, can interfere with developmental brain sterol biosynthesis (45–51). Some medicines might directly inhibit key enzymes involved in sterol biosynthesis, while others could interfere with biosynthesis by altering gene expression, affecting the availability of substrates, or disrupting regulatory pathways (51). Regardless of the specific mechanisms involved, the consequences of disrupted sterol homeostasis can impact normal brain function in either case.

To date, over 30 prescription medications have been described as having post-lanosterol biosynthesis inhibiting side effects (52, 53). Aripiprazole, cariprazine, trazodone, and haloperidol have been the most extensively studied regarding their effects on sterol biosynthesis (46, 48, 54, 55). While they do not have a high degree of structural similarity or mechanism of action (except aripiprazole and cariprazine), they share a common biochemical signature and are all CNS-targeting medications. They are all DCHR7 inhibitors during development with a chemical signature that includes elevation of 7-DHC, 8-DHC, and 7-DHD and decreased desmosterol and cholesterol (52). These findings have also been validated across *in vitro* systems (52, 53, 56), rodent experiments and tissue types (45, 46, 48, 49), and analyses of blood samples from psychiatric patients and women of reproductive age (47, 54).

Single-Allele DHCR7 Pathogenic Variants Represent a Latent Vulnerability

Rodent transgenic models and in vitro human fibroblast cultures suggest that the DHCR7 genotype matters regarding the magnitude of sterol inhibition (54). Pathogenic variants of the *DHCR7* gene, present in approximately 1%–3% of the human population (57, 58), might not be sufficient to produce a disease but represent a latent vulnerability. More than 200 likely pathogenic variants of DHCR7 have been identified to date (59, 60). While the exact pathogenic variants might vary in frequency across different populations, the overall frequency of vulnerability appears to be comparable across sex and ethnic groups, with perhaps the exception of East Asian and Korean populations (0.5%–1%) (61). DHCR7± individuals have increased baseline 7-DHC levels. When their human fibroblasts are exposed to medications with sterol-inhibiting side effects, the sterol biosynthesis disruption reaches a magnitude close to that seen in patients with SLOS (50, 54). Rodent transgenic findings on Dhcr7± mice also confirmed these findings, providing additional insights into the potential underlying pathophysiology. Namely, a maternal exposure model revealed that both maternal and offspring Dhcr7± heterozygosity conferred vulnerability: Dhcr7± pups born to Dhcr7± mothers showed the highest sterol biosynthesis disruption in repose to aripiprazole, trazodone, and cariprazine (45, 46, 48). Thus, it appears that, at least in experimental systems, genetic vulnerability and chemical inhibition synergize, with yet unknown consequences on human health. The mechanism by which this gene–medication interaction occurs remains unknown, and this might be different for the various compounds that can inhibit sterol biosynthesis. Namely, while the pathogenic genetic variant will reduce the availability of the DHCR7 enzyme, the medications can either directly inhibit the same enzyme, inhibit another upstream enzyme in the post-lanosterol biosynthesis pathway, or interfere with genes belonging to networks responsible for sterol enzyme biosynthesis, degradation, or turnover. Ultimately, elevated 7-DHC and related oxysterol levels have substantial biological activities, including inhibiting Hedgehog response (62, 63), a key driver of normal brain development. Similarly, the p75 neurotrophin receptor expression depends on the cholesterol biosynthesis machinery (64).

Sterol Biosynthesis Inhibiting Polypharmacy Effects are Synergistic or Summative

We live in the age of polypharmacy, a nationwide and worldwide challenge (65–67). Polypharmacy is increasingly common in the United States and contributes to the substantial burden of drug-related morbidity. Quinn and Shah counted the incidence of multidrug combinations observed in 4 billion patient-months of outpatient prescription drug claims from 2007–2014 in the Truven Health MarketScan Databases (65). They found that among patients taking any prescription drug, half were exposed to two or more drugs, while 5% were exposed to eight or more. Notably, CNS polypharmacy is particularly commonly seen in the treatment of mental illness (68).

If genetic Dhcr7± vulnerability and chemical inhibition of sterol biosynthesis synergize, could two or more medications with sterol-inhibiting side effects have a similar, synergistic, or summative effect? In vitro, rodent, and human biomaterial studies suggest this might be the case (69, 70). Neuronal and astrocytic cultures treated with ARI+TRZ showed an additive effect, increasing the 7-DHC/CHOL ratio by 15- to 20-fold over vehicle-treated cultures. In addition, adult mice treated with ARI+TRZ polypharmacy affected multiple organ systems of the body, leading to decreased proliferation and reduction of neural progenitor cells in the hippocampi of male adult mice and decreased expression of microglial marker IBA1 in the brain (69, 70). Furthermore, in a study of pregnant women taking prescription medications, it was reported that women taking more than one medication with 7-DHC–elevating side effects had the highest 7-DHC levels in their blood, suggesting a synergistic or summative effect of polypharmacy (47).

This raises the question of when and where will the polypharmacy effects summate or synergize. The drugs that show synergy have different mechanisms of action, most commonly mediated through a specific receptor. If at least one medication's inhibition of post-lanosterol enzymes is receptor-based (and not direct chemical inhibition), the overlapping receptor distribution will define the site of most substantial synergy. In the case of nonoverlapping receptor distribution, synergy or summations would not be observed; instead, it would affect a broader tissue distribution where either one of the receptors is expressed. This could give rise to a very different phenotype and suggest that each combination of polypharmacy could have different ultimate consequences. Should this be the case, this would be further complicated by the developmental

timing of receptor expression vs. the timing of polypharmacy. Thus, the same combination of sterol-inhibiting polypharmacy could differently affect different organs, regions, or cell types based on their dose, timing of polypharmacy, receptor expression pattern, mechanism of action, developmental stage, genotype, and many other factors.

There are Likely to be Multiple Developmental Vulnerability Periods to Post-Lanosterol Inhibition

The vast majority of post-lanosterol inhibition data obtained to date has focused on intrauterine development and maternal intake of medications during pregnancy. However, many infants might be potentially treated with (known or yet unknown) medications that could inhibit sterol biosynthesis. Early postnatal development is also likely to be a critical vulnerability window (71) as this is a period of progressive myelination and development of glial cells, both highly sterol-dependent processes. Furthermore, puberty is a period of rapidly changing hormonal homeostasis, synaptic pruning, and continued myelination, all strongly influenced by sterol biosynthesis (72, 73). This is also a period where physicians are more likely to prescribe medications with sterol-inhibiting side effects. The overall and specific medication effects causing partial sterol inhibition are almost entirely unknown in these postnatal vulnerability periods. Yet, the detrimental effects of post-lanosterol inhibition would not result in dysmorphologies seen during fetal development but could have functional consequences. Namely, interference with myelination and synaptic pruning, both sterol biosynthesis-dependent processes, could result in changes in functional connectivity. Such disruptions would ultimately result in learning difficulties, emotional disturbances, developmental delay, language acquisition challenges, or behavioral alterations.

Differential Effects of *DHCR7* Inhibition in Tissue and Cell Types

While representing only 2% of body weight, the brain contains 25% of the body's cholesterol and sterol derivatives. However, brain sterol biosynthesis is not homogenous across brain regions. For example, cholesterol in the pons and cerebellum is ~2.5 times higher than in the neocortex (74). Furthermore, *in situ* hybridization for post-lanosterol biosynthesis enzymes reveals markedly different expression levels across cell types, with very high expression in the principal neurons of the hippocampus (64) and serotoninergic cells. This later is also underscored by a functional vulnerability of *Dhcr7*± mice, revealing an increased head-twitch response to the 5-HT2A agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (75). These findings have several potentially significant implications. First, the brain is likely the most sensitive organ to developmental sterol inhibition. Second, it is likely that brain regions that have the highest enzyme expression and sterol production are the most likely affected by sterol inhibition. Third, as developmental sterol accumulation proceeds differently across the different brain regions, the same sterol-inhibiting medication, given at other times, might affect different brain structures. Fourth, high 7-DHC levels are likely to affect the various brain cell types differently, perhaps regulated by their neurochemical content. Finally, when discussing the effects of post-lanosterol biosynthesis disruption, one must consider that sterols might be synthesized in one cell or region. Still, they are also actively trafficked to all parts of the brain and interchanged between glial and neuronal cells (76).

There is Still a Significant Amount of Critical Knowledge Missing

While there is plenty of evidence suggesting a cautionary approach when using medications with sterol-inhibiting side effects during pregnancy, there are significant gaps in our current data.

1. We have limited knowledge of how these medications interfere with developmental sterol biosynthesis. The mechanism might be direct inhibition of the enzyme(s) or receptor-mediated, and such information would be essential to obtain.
2. While we understand that DHCR7 single allele pathogenic variants might potentiate the effects of sterol inhibiting effects, such synergy has not yet been investigated for single copy pathogenic alleles in genes encoding other post-lanosterol enzymes (e.g., DHCR14 or EBP).
3. We do not understand the effects of elevated 8-DHC and 7-DHD and their oxysterols. Based on their chemical structure and properties, they are very likely to be abundant and biologically active, but no such information is available to date (29).
4. The exact time window of a potential developmental vulnerability remains unknown, as is the dose and duration of medications that could cause potential harm.
5. We do not know whether there is a critical threshold or concentration of 7-DHC (or oxysterols) that becomes harmful to the developing baby's brain or other tissue (31).
6. Can co-morbidities also synergize with medication-induced inhibition of sterol biosynthesis, like polypharmacy and Dhcr7 genotype? Diabetes, pre-eclampsia, metabolic conditions, and lifestyle factors could theoretically make the developmental outcomes of sterol inhibition much worse.
7. We are exposed to hundreds of chemicals throughout our daily lives, and some of them have sterol inhibition properties (51, 53, 77, 78). Do these chemicals predispose to developmental disabilities, in particular, if they are combined with the already identified sterol-inhibiting genetic factors or prescription medications?
8. Commonly used medications can potentially inhibit other enzymes in the post-lanosterol biosynthesis pathway (51). For example, amiodarone alters cholesterol biosynthesis through the inhibition of EBP and dehydrocholesterol reductase 24 (DHCR24), both of them post-lanosterol enzymes (79). Yet, this is a greatly understudied area.
9. A recently identified Fetal Fentanyl syndrome (FFS) (80) arising in newborns born to mothers with nonprescription fentanyl use has a remarkable phenotypic and biochemical similarity to SLOS. This suggests that FFS partially arises from sterol inhibition (81). Furthermore, a recent review found that 10 of 12 case-control and 7 of 18 cohort studies documented statistically significant positive associations between maternal opioid use during pregnancy and congenital malformations (82). Are these dysmorphologies a result of sterol biosynthesis inhibition, or are they arising through an unrelated mechanism (83)?
10. Are there deleterious consequences of long-term use of medications with sterol-inhibiting side effects for adults? Low cholesterol levels appear to be associated with an increased risk for depression (84, 85, 13, 12). Furthermore, a recent study evaluating interactions between antipsychotics and medications used in the treatment of cardiovascular disease reported the highest number of interactions among beta-blockers and antipsychotics (66). Remarkably, the combinations that reported the most common adverse outcomes included the medications that have been previously identified as having 7-DHC–elevating side effects – including metoprolol and nebivolol (49).

Potential Clinical Implications and Recommendations for Policies and Future Research

Based on the above-presented cautionary findings, we believe that in clinical practice, several approaches are warranted:

- Pregnant mothers with *DHC7*± genotype should not be utilizing medications with 7-DHC–elevating side effects. There are usually safe alternatives to these medications, so this approach should rarely interfere with the best patient treatment.
- We recommend genetic testing of pregnant women who must utilize medications with sterol-inhibiting side effects. If prenatal testing is also performed, it is imperative to gain insight into the *DCHR7* status of the unborn child. This is especially important when the unborn child and mother carry single-allele *DCHR7*± pathogenic variants, as these babies might be the most vulnerable to post-lanosterol biosynthesis disruptions.
- Patients with SLOS should never receive medications with 7-DHC–elevating side effects.
- Clinicians should be educated about the potential danger of medications with DCHR7-inhibiting side effects for the developing brain. During pregnancy (and potentially during other vulnerability periods), they should avoid prescribing polypharmacy that shows potential synergistic interaction on the post-lanosterol biosynthetic pathways. It is rarely appreciated that 7-DHC–elevating medications might target

different organ systems (e.g., psychotropic and cardiac medications – trazodone + metoprolol), yet their unwanted effects might converge on the same biochemical pathway.

National regulatory organizations should pay close attention to all the above-listed findings and develop or revise knowledge-based guidelines for utilizing such mediations. Furthermore, pharmaceutical companies should routinely assess newly developed (and perhaps already approved) medications for their effects on developmental sterol biosynthesis. In addition, national funding agencies should invest in research to find definitive answers to these essential public health questions. With the rapid emergence of new technologies such as *in situ* metabolomics and lipidomics (74, 86), bioinformatics, new model systems [including induced pluripotent stem cells (iPSCs) (87) and humanized mice], and novel, high-resolution imaging technologies, we should be able to gain a more definitive insight in the risk-reward equation for each medication and develop a safe, personalized treatment plan for our patients.

Conclusions

Unintended sterol inhibition by many prescription medications is well documented, and it is a potential cause for concern when used during pregnancy. Nevertheless, it should be acknowledged that many of the findings presented above are obtained using in vitro and transgenic rodent models. While the post-lanosterol biosynthetic pathway is highly conserved between rodents and humans, it is uncertain which of those findings translate to the human population. For each individual, the magnitude of sterol disruption (and potential consequences for the unborn child) will likely depend on lifestyle, dosage, potential polypharmacy, genetic makeup, and other possible factors. Nevertheless, the above-presented data advises caution and a conservative approach in the use of medications with sterol-inhibiting side effects during pregnancy.

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Author Contributions

K.M. and Z.K. obtained many of the presented results, discussed the findings, and wrote the manuscript together. Both authors have read and approved the manuscript. The authors take full responsibility for all data, figures, and text and approve the content and submission of the study. No related work is under consideration elsewhere. Corresponding author: Prof. Mirnics for all aspects of the presented work.

Author Disclosures

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