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Brain Medicine

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EDITORIAL

Medication-induced sterol disruption: An overlooked threat to brain development and public health

Brain Medicine March 2025;1(2):1–3; doi: https://doi.org/10.61373/bm025d.0041

Scientific progress often demands that we revisit comfortable assumptions. Occasionally, new data do more than inform—they provoke. The article by Korade and Mirnics in this issue of *Brain Medicine* is a rare and necessary provocation (1). It unveils a silent hazard: that a broad array of widely prescribed drugs, developed and approved for disparate conditions, may converge on a shared off-target toxicity. These medications disrupt sterol biosynthesis—an essential metabolic process underpinning neural development—and do so in ways that mirror the biochemical footprint of devastating genetic syndromes.

Cholesterol, a molecule that has captivated scientific inquiry for generations, stands among the most intensely studied compounds in history—as evidenced by the thirteen Nobel laureates whose distinguished careers were significantly devoted to unraveling its mysteries (2).

While clinical discourse often portrays cholesterol as a cardiovascular villain, its role in the brain reveals a profoundly different narrative. Within this delicate neural landscape, cholesterol emerges not as an adversary but as an indispensable element—a fundamental cornerstone of cerebral architecture without which life itself could not exist. The brain contains a disproportionate 25% of the body's cholesterol, despite accounting for only 2% of total mass (3). This is not incidental—it is the molecular scaffolding upon which brain architecture and connectivity are built. Cholesterol is central to synapse formation, axonal guidance, dendritic arborization, and myelin integrity. Cholesterol and sphingolipids, embedded within membrane raft microdomains, serve as critical signaling molecules that facilitate neuronal differentiation and synaptogenesis, making their proper metabolism essential for maintaining brain function and preventing neurological and neurodegenerative diseases (4). It is actually fascinating that two decades ago there was a race to identify a glia-derived factor that strongly promotes synapse development in cultures of purified CNS neurons. Mauch et al published a paper in Science in 2001 identifying this factor as cholesterol complexed to apolipoprotein E-containing lipoproteins (5). It is therefore not surprising that cholesterol homeostasis is so critical that the brain maintains an autonomous cholesterol economy, isolated by the blood-brain barrier from systemic fluctuations.

From early gestation to late adulthood, this self-contained biosynthetic machinery sustains cognitive and neural function. Genetic disruptions of this pathway—such as in Smith-Lemli-Opitz Syndrome (SLOS), lathosterolosis, desmosterolosis, CDPX2, CHILD syndrome, SC4MOL deficiency, and HEM dysplasia, all caused by pathogenic variants in critical sterol biosynthesis genes—produce catastrophic developmental outcomes (6, 7). This has long served as a warning: perturbing sterol homeostasis in the developing brain is not compatible with health.

Korade and Mirnics have a strong record in this area (8) and what their work has highlighted is profoundly unsettling. Over 30 FDA-approved drugs—among them, psychiatric mainstays such as aripiprazole, trazodone, haloperidol, and cariprazine—have been shown to inhibit DHCR7. This inhibition raises the levels of 7-dehydrocholesterol (7-DHC), suppresses cholesterol synthesis, and generates a sterol profile indistinguishable from that seen in congenital metabolic disorders. This is not a hypothetical concern—it is empirically validated in cell lines, rodent models, and human blood samples. Notably, a comprehensive, systemic review by Bolland and Tatonetti investigated the fetal outcomes following prenatal exposure to DHCR7 modulators, and conceded that *"first-trimester exposure to DHCR7 inhibitors resulted in outcomes similar to those of known teratogens"* in humans (9).

Even more alarming is the fact that 7-DHC is not inert. It is biochemically volatile—the most oxidizable lipid known in humans with a reactivity 200 times greater than cholesterol. Its accumulation results in the formation of toxic oxysterols such as DHCEO, which impair neurite outgrowth, alter cellular morphology, and damage the fundamental architecture of neuronal connectivity (7, 10, 11). These are not esoteric molecular details. These are mechanisms of harm.

The scenario becomes even more concerning when one considers the effect of polypharmacy. In experimental systems, combinations of two or more DHCR7-inhibiting drugs elevate 7-DHC to levels more than 15 times above control (12, 13). Pregnant women taking multiple such medications exhibited the highest concentrations of 7-DHC in their blood. These effects are not additive—they are often synergistic. And they are happening under the radar of our regulatory systems.

Here, we encounter a pivotal failure in modern pharmacology: regulatory drug approval is based almost exclusively on single-agent safety data, despite the clinical reality that it has become increasingly common for patients to rely on the use of multiple prescription medications (14, 15). Preclinical toxicology, clinical trials, post-marketing surveillance—all assume that medications will be taken in isolation. But that assumption collapses in real-world clinical settings. Most patients—especially those with chronic psychiatric or medical conditions—take multiple drugs simultaneously. Yet these combinations are typically not tested together, not even in animals, let alone in pregnant women or infants. This is a blind spot of breathtaking scale.

What Korade and Mirnics reveal is especially disturbing in this context. If individual drugs can mimic a metabolic disorder, what are we to make of their interactions? We are prescribing molecular cocktails with no empirical knowledge of how they alter developmental neurochemistry. The combinations that are most common in clinical practice are also the least studied. This is not an oversight. It is a systemic design flaw in how we evaluate drug safety (see Fig. 1).

And the vulnerable populations are not hypothetical. At least 1–3% of the general population carry single-allele DHCR7 mutations (16). These individuals are typically asymptomatic, but they live on the edge of sterol balance. A single prescription can tip that balance. Two or more may send them into a biochemical state that resembles SLOS. Neither the clinician nor the patient would ever know.

Moreover, the developmental windows of vulnerability extend well beyond gestation. Myelination, glial proliferation, synaptic pruning, and hormonal shifts occur through infancy, childhood, and adolescence (17). These stages are marked by high demand for sterol-derived signaling and membrane components (18). The sterol-disrupting effects of drugs administered during these periods may manifest not as malformations

Received: 25 March 2025. Revised: 3 April 2025. Accepted: 5 April 2025.
Published online: 22 April 2025.

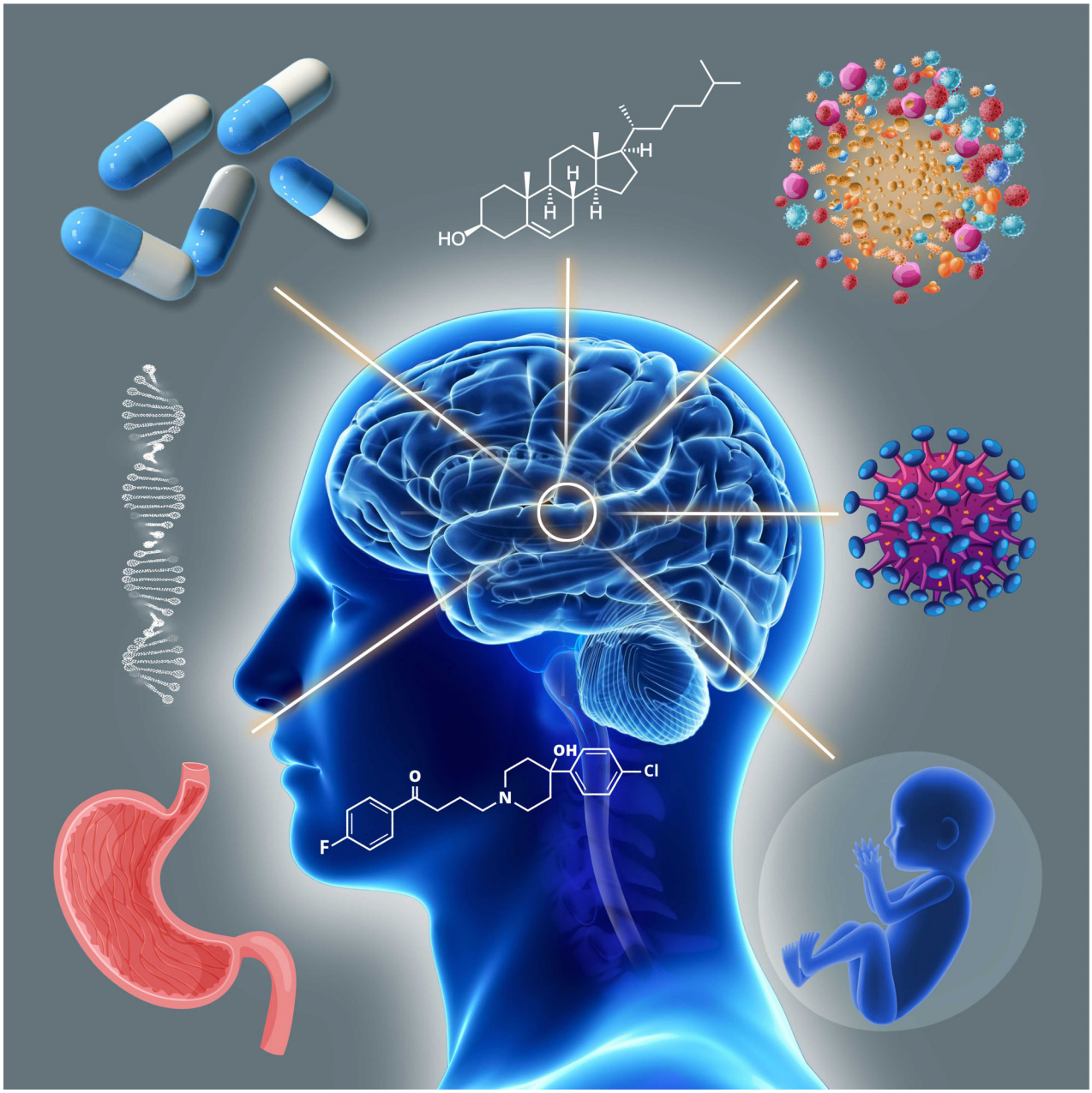

Figure 1. Medication-induced disruption of sterol biosynthesis poses significant risks to brain development and function. At the top center of this schematic lies the cholesterol molecule—an anchor of neurobiological integrity—flanked by the structure of haloperidol embedded within the brain, exemplifying one of over 30 FDA-approved compounds known to inhibit DHCR7. These agents, many of which are orally administered and processed through the gastrointestinal–hepatic axis, initiate biochemical disruptions at the level of first-pass metabolism, altering sterol homeostasis before the compounds even reach the central nervous system. The result: accumulation of toxic precursors such as 7-dehydrocholesterol (7-DHC) and their conversion into highly reactive oxysterols (top right), with well-established neurotoxic potential. On the left, a DNA strand signals genetic vulnerability, which can amplify these pathological cascades—particularly during periods of neurodevelopmental sensitivity (lower right). The diverse array of medications (pills, upper left) underscores the wide pharmacologic footprint of this off-target effect, raising serious concerns about additive or synergistic toxicity in the context of polypharmacy. Taken together, this mechanism—once overlooked—demands urgent attention as a pressing public health concern, particularly for developing brains and genetically susceptible populations.

but as subtler, chronic, functional impairments: cognitive delay, emotional dysregulation, behavioral disturbance. We are not tracking these outcomes. We are not even looking.

The implications are immense. The pharmaceutical industry must immediately incorporate sterol biosynthesis screening into all developmental safety assessments. Regulatory agencies must abandon the fiction of monotherapy testing and require at least some modeling of common drug combinations. Clinical trial designs must evolve to reflect the messy reality of modern medicine. And post-marketing surveillance must include not only short-term adverse events but also long-term developmental and behavioral endpoints.

Clinicians, too, must respond with heightened vigilance. Genetic testing for DHCR7 pathogenic variants (and other post-lanosterol biosynthesis enzymes) should be considered in women of childbearing age who require medications known to disrupt sterol synthesis. Polypharmacy involving such drugs should be avoided during pregnancy

whenever possible. Patient counseling must include discussions of these risks—especially in psychiatric care, where these medications are often initiated early and continued long-term.

Korade and Mirnics are not offering a mere caution. They are challenging the very architecture of how we think about drug safety. The problem they highlight is not that a few drugs have an unfortunate side effect. It is that our entire system of medication evaluation ignores the complexities of developmental biology, genetic susceptibility, and real-world prescribing patterns.

We must no longer regard sterol biosynthesis as an obscure metabolic pathway. It is a central axis of brain development. And the disruption of that axis—whether by mutation, medication, or both—has consequences that are profound, irreversible, and avoidable. Despite decades of pharmaceutical development, we lack a comprehensive catalogue of FDA-approved medications with sterol-inhibiting side effects—a critical knowledge gap that may obscure iatrogenic disruptions of this essential pathway.

This is a call to action. Not someday. Now.

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