

5th International Conference on

HIV/AIDS, STDs and STIs

November 13-14, 2017 Las Vegas, Nevada, USA



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Unraveling the complex psychopharmacology associated with the adverse neuropsychiatric side effects and recreational use of HIV-1 antiretroviral drugs

Efavirenz has been a mainstay of HAART since its introduction in 1998. Though recently downgraded by DHHS from a first-line to an alternative treatment due to risk of neuropsychiatric adverse events (NPAE), both WHO and South African guidelines continue to recommend efavirenz as the preferred NNRTI for HAART in adults and generic forms are becoming available. Yet, only recently has significant progress been made towards a molecular mechanistic appreciation of efavirenz-mediated NPAEs and its attractiveness as a recreational drug. Contributing factors are rapid brain accumulation and a narrow therapeutic window. Receptor pharmacology studies indicate that within a concentration range relevant to its brain exposure, efavirenz disrupts dopaminergic, serotonergic, cholinergic and GABAergic systems. Hence, the combined effects on these neurotransmitter systems is likely to be responsible for some of efavirenz's NPAEs, such as sleep disturbances, depression, anxiety, hallucinations, dizziness, headaches and memory impairments. Specifically, a number of CNS off-target interactions for efavirenz have been identified, including with the 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, M₁, M₃ and GABA-A receptors, DAT, SERT and VMAT2 transporters and MAO-A. In rats trained to discriminate LSD from saline, efavirenz partially substitutes for LSD and this substitution is blocked by pre-treatment with a 5-HT_{2A} receptor selective antagonist. Efavirenz also apparently competes for the same binding site at the 5-HT_{2A} receptor as LSD and prolonged chronic treatment with efavirenz drastically reduces 5-HT_{2A} receptor levels. Findings from our receptor pharmacology studies and those in animals and humans correlate primarily with behavioral effects related to depressive, anxiogenic, hallucinogenic and sleep disturbances.

Biography

John A Schetz is a Professor of Pharmacology, Neuroscience and Medical Education with a penchant for advancing knowledge and addressing societal needs of relevance to medicine. His translational research efforts focus on elucidating mechanisms of drug action and discovery and development of innovative agents for preventing or treating neurological and psychiatric conditions. His research has been published in reputed journals and featured nationally and internationally in print, radio and televised media reports. His collaborative team pioneered a molecular mechanistic understanding of adverse neuropsychiatric events associated with efavirenz when taken as prescribed and its attractiveness as a recreational drug when smoked.

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