

PREFACE: SPECIAL ISSUE ON CHALLENGES AND NEW FINDINGS ON MISUSED PSYCHOACTIVE DRUGS

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PREFACE

Studying misused psychoactive (psychotropic) substances is a never-ending, challenging, and fascinating task. From the most commonly used natural substances, such as alcohol, tobacco, and cannabis, to the newest synthetic opioids and stimulants, we continue to learn how they act and why they can profoundly alter human lives. Regardless of their origin (natural or synthetic) or chemical structure, these substances stimulate brain regions associated with emotions, perceptions, and memory. Most have rewarding effects because they activate the mesolimbic system, thus increasing levels of dopamine, a powerful chemical brain signal to repeat the behavior that led to such an increase. A few others (classic hallucinogens) do not.

Repeated psychoactive substance misuse can result in serious adverse effects. Some are well known, like respiratory problems in chronic tobacco users or malnourishment in people with alcohol use disorders. Others have only been recently described, such as the neuro-inflammatory actions of misused substances. In addition, current delivery methods (e.g., vapers), purest forms (e.g., cannabis concentrates), and the constant appearance of rapidly evolving synthetic molecules

present challenges to research, prevention, and treatment not seen before.

Repeated use of misused psychoactive substances can lead to tolerance to their desired effects and addiction, a complex disorder that involves changes in the brain and behavior. This condition is characterized by continued substance use despite being aware of adverse effects and wanting to quit. Such a contradiction emerges from complex structural and functional brain changes. In particular, people with addiction have an imbalance between the limbic system responsible for impulsive behavior and the supra-limbic brain regions (e.g., prefrontal cortex) that modulate higher-order cognitive functions, such as planning, decision-making, and social behavior. Understanding the nature of these changes and the adverse health consequences associated with substance use disorders is the first step for addressing them effectively.

Recent research has focused on benefiting from psychoactive substance use under controlled conditions. Possibly, the best examples are the development of pharmaceutical products with Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) for treating specific disorders, and using ketamine for major depressive disorder with suicidal thoughts.

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This special issue includes six reviews on the effects and mechanisms of action of opioids, cannabinoids, alcohol, amphetamines, nicotine, and hallucinogens. The first article presents an overview of the emergence in the drug market of potent synthetic opioids such as fentanyl, fentanyl derivatives, and non-fentanyl new psychoactive opioids, as well as their role in the current opioid crisis. The second paper explores the risks and therapeutic uses of THC and CBD, the best-studied phytocannabinoids in the marijuana plant. The next review describes how alcohol alters the immune system and the mechanisms responsible for alcohol-induced carcinogenesis and tumor growth. Information on the effects of crystal meth and other synthetic amphetamine-type stimulants, including cathinones, is included in the fourth review.

The fifth article addresses the challenges associated with using electronic systems to deliver nicotine and other substances, the increased prevalence of vaping, and the adverse health effects of this practice, highlighting the dangers of polydrug use. The final paper examines the renewed interest in the study of hallucinogen drugs (both from users and researchers), how main hallucinogen drugs work, their risks, and their therapeutic potential. Each paper contains tables and figures to complement the concepts presented in the text.

As the Guest Editor, I would like to thank the Editors of *Revista de Investigación Clínica-Clinical and Translational Investigation* – for their kind invitation to coordinate this special issue, and the authors, for sharing their expertise on the topics covered here.