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POSTCOVID-19 WAR Era, Different Pharmacotoxicologic (Re) Actions Updates, Toxic Synergies, and How Drug Abuse Exacerbates Burdens

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Editorial

Recently it became obvious that drug abuse, infectious disease, and hematologic dysregulation are not peripheral concerns—they are central determinants of therapeutic success or failure. Late-stage metastatic cancer remains one of the most pharmacologically unforgiving landscapes in modern medicine. Despite decades of therapeutic innovation, the microenvironments that support disseminated tumor cells have evolved into highly specialized, treatment-resistant ecosystems. These niches—shaped by chronic inflammation, stromal reprogramming, immune exhaustion, and metabolic rewiring—are notoriously refractory to cytotoxic agents and androgen-receptor (AR) pathway intensification strategies. Yet an under-recognized accelerant of this resistance is emerging: the rising global burden of drug abuse and its profound pharmacotoxicological consequences.

What is Known?

Different Lancet, Nature, and clinical literature highlighted a critical balance in cancer care, oncology, and potent analgesics, which are essential for pain relief. However, (un)known drugs might carry a significant risk of addiction and collateral damage. Besides, severe pains have debilitating effects; they suggested that exaggerated drug abuse could result in risky patients' Medicare and Medicaid, eventually [1–5]. Substance misuse is not merely a parallel public-health crisis; it is a biological force multiplier. Drugs of abuse reshape hematologic, immunologic, and metabolic systems in ways that directly undermine cancer therapies, distort diagnostic signals, and potentiate toxicity when combined with multi-agent regimens. As drug stacking becomes increasingly common—both in recreational settings and in late-stage oncology—therapeutic windows narrow, adverse events intensify, and the line between treatment and toxicity blurs. Our last decade publications introduce different evidence-based model systems for studying diabetes, cancer and carcinogenic processes, infectious diseases, and their bidirectional interactions with hematologic blood cells, provide a timely framework for understanding these converging crises [6–8]. These models reveal how drug-induced perturbations in blood-cell biology can amplify metastatic resilience, obscure clinical interpretation, and heighten the risk of catastrophic pharmacologic interactions.

What is unknown? How a perfect storm, and drug abuse/ misuse might also generate metastatic resistance, for example, in cancer patients. The metastatic microenvironment is inherently hostile to therapeutic penetration, hypothetically. Hypoxia, extracellular-matrix density, aberrant vasculature, and stromal shielding collectively reduce drug accessibility, by definition. Meanwhile, AR-pathway intensification—central to prostate and other hormone-responsive cancers—faces diminishing returns as tumors evolve toward a ligand-independent (in)activation, splice-variant signaling, and cross-talk with (pro- inflammatory pathways [4–9]. Recall that frequent drug abuse compounds these challenges through several mechanisms i.e. immunologic suppression— for instance opioids/ stimulants, and cannabinoids dysregulate neutrophil and lymphocyte function, impairing anti-tumor immunity [3–5,9].

Besides, as previously described, hematologic distortion of Thrombosis and Hemostasis (T&H) is also sensitive (in)direct player [6–8]—substances such as cocaine, methamphetamine, and synthetic opioids induce leukocytosis, thrombocytopenia,

or dysfunctional erythropoiesis, complicating interpretation of disease progression [5–7]. Metabolic interference—alcohol and stimulants alter hepatic enzyme systems, accelerating or inhibiting drug metabolism unpredictably. Moreover, different inflammatory priming and chronic drug exposure might increase different cytokines, which are already key drivers of metastatic niche formation, theoretically [9]. All the abovementioned effects have not only an additive but also, they can collaborate, synergistically. Subsequently, potential metastatic niche thrives on dysregulation, while drug abuse provides precisely the systemic chaos that allows resistant clones to flourish. Besides, in late-stage cancers, (and palliative terminal phases) polypharmacy is unavoidable and make drugs misuse an uncontrollable (re)action.

Patients often receive combinations of cytotoxics, AR-pathway inhibitors, corticosteroids, antibiotics, anticoagulants, and supportive-care agents simultaneously. When recreational substances enter this pharmacologic ecosystem, for example, the result is a stacking phenomenon—a convergence of metabolic, immunologic, and neurologic interactions that can transform therapeutic regimens into toxic cocktails, however.

It is essential to update and upgrade many aspects of medical errors-triangle which treating Physicians-patients- and pharmaceutical companies play (un)known role as the main cause of many preventable deaths. Four important potential players prerequisite to be updated:

Cytochrome P450 overload

Many abused substances are potent modulators of CYP enzymes i.e. Cocaine and methamphetamine induce CYP3A4 and CYP2D6, destabilizing dosing of AR-pathway inhibitors. Besides, alcohol competes for CYP2E1, altering acetaminophen and chemotherapeutic metabolism. Moreover, Cannabinoids inhibit CYP2C9 and CYP3A4, raising plasma levels of cytotoxics. In metastatic diseases, where therapeutic indices are already narrow—these shifts can precipitate to significant organ failure, hematologic collapse, or lethal arrhythmias [1–9].

Neuro-immunologic crosstalk

Stimulants and opioids alter neuro-immune signaling, reducing the efficacy of immunotherapies and accelerating metastatic spread. Drug-induced microglial activation, for example, can promote brain metastasis by weakening blood–brain barrier integrity and metabolic disorders, however.

Hematologic vulnerability

Our model systems described/ highlight how hematologic cells act as both sensors and amplifiers of systemic stress [6–8]. Drug abuse hypothetically disrupts neutrophil extracellular trap (NET) formation, alters monocyte differentiation, and induces platelet hyperactivation. These changes not only increase thrombotic risk—a major cause of mortality in metastatic cancer—but also distort biomarkers used in clinical decision-making, as well. A critical but often overlooked dimension of the abovementioned mistakes is Pro-Diagnostic biases. Many legacy clinical algorithms and laboratory reference ranges were developed decades ago, long before the current landscape of widespread drug poly-use, synthetic-drug proliferation, and complex metastatic biology generated. These mismatches lead to several failures unequivocably; causing misinterpretation of hematologic indices, and drug-induced for example, leukocytosis or thrombocytopenia, which may be mistaken for infection, treatment toxicity, or disease progression. Conversely, drug-suppressed immune markers may mask early signs of metastasis or sepsis, speculatively. Furthermore, traditional liver-function tests cannot reliably distinguish between alcohol-induced hepatotoxicity, chemotherapy-induced injury, and/or metastatic infiltration, controversially; causing an inadequate toxicology screening. Most oncology workflows do not routinely screen for recreational substances, despite their profound impact on treatment safety. This omission perpetuates a cycle of misdiagnosis, inappropriate dose adjustments, and preventable toxicity. Our R&D's team in our recent publications argued convincingly that modern diagnostics must incorporate dynamic, systems-level models—particularly those that integrate hematologic cell behavior, infectious-disease interactions, and drug-induced perturbations [6–8]. Without such tools, clinicians are (not) effectively navigating disease progression with outdated maps, and legacy diagnostics SOPs.

It is known that drug abuse is a well-established risk factor for infectious diseases, including viral hepatitis, HIV, bacterial sepsis, and opportunistic infections [4,9]. In metastatic cancer, these infections are not merely comorbidities—they are active participants in pharmacotoxicology, eventually.

Our model systems from 2018–2019 (prepandemic periods) demonstrate how infectious agents reshape hematologic cell behavior in ways that mimic or mask, for example cancerogenic processes. When layered on a top drug-induced hematologic distortion/side effects, the diagnostic picture becomes nearly unreadable and might cause bias-based (re)action. As observed after COVID-19 mutants' attacks, new variants did not follow old-fashioned screening tests, however.

The convergence of drug abuse, metastatic resistance, and diagnostic biases demands a new conceptual framework—one that views the patient not as a passive recipient of therapy but as a dynamic biological system shaped by environmental, behavioral, and pharmacologic forces.

My proposed model system (did) offers a blueprint for such integrations. By capturing the bidirectional interactions between cancer cells, infectious agents, and hematologic components, these models illuminate how drug-induced perturbations ripple through the metastatic ecosystem [6,7].

Besides, "hypothetically" key principles for a modernized framework might lie on the systems-level diagnostics that incorporate hematologic behavior, immune profiling, and toxicology data. On the other hand, making dynamic risk modeling accounts for recreational drug (ab)use, polypharmacy, and metabolic variability can upgrade old-fashioned perceptions, sooner or later. Hence, focusing on the microenvironment-targeted therapies, which are designed to overcome drug-induced resistance pathways, might additively affect many (un)known side effects, prophylactically. It is essential to understand that "precision toxicology" should be integrated in modern diagnostics to identify early signs of stacking-related organ distress. On the other hand, an integrated addiction-oncology care, appropriate temporal and special pain management, and recognizing substance misuse as a biological modifier of treatment outcomes, are very important key players, which should be held as modernized upgrades, eventually. Take home message is that there is urgent need for a paradigm shifts, in (ab)using certain drugs especially anti-infectious, anticancer and anti-pains(analgetic) managements.

The intersection of drug abuse and metastatic cancer is not a fringe issue—it is a growing clinical reality. As recreational drug landscapes evolve and late-stage cancer therapies become increasingly complex, the risk of pharmacotoxicological catastrophe rises. Drug stacking, once a term confined to recreational subcultures, now describes a dangerous overlap between therapeutic necessity and behavioral vulnerability. Our R&D's studies underscore a critical truth that we cannot treat (metastatic cancer) patients effectively without understanding the systemic forces, which shape their (patho-) biology and pains, (in)directly. Key takeaway would be that drug abuse, infectious disease, and hematologic dysregulation are not peripheral concerns—they are central determinants of therapeutic success or failure.

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