documented and serious complication of this drug (and cocaine adulterant). Patients may present with a variety of neurologic symptoms related to multifocal white matter lesions that can be identified on magnetic resonance imaging. The lesions do not appear to be vasculitic and are often reversible with cessation of levamisole exposure. In the setting of cocaine abuse, the clinical and magnetic resonance imaging features can be confused with other complications of cocaine abuse and high-risk lifestyles.²⁻⁴

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In reply: We appreciate Dr Graebner's comments regarding levamisole-induced leukoencephalopathy, a well-documented complication of levamisole when used in high doses for treatment of conditions such as malignant melanoma or severe recurrent aphthous ulcers.^{1,2} During the drafting of our manuscript,³ the association between leukoencephalopathy and levamisole-contaminated cocaine had not been reported in the literature. Since then, one article has raised the possibility of multifocal inflammatory leukoencephalopathy resulting from levamisole-adulterated cocaine, suggesting that this complication can also occur with small amounts of levamisole found in cocaine.⁴ We encourage health care professionals to add leukoencephalopathy to the growing list of complications resulting from this adulterant frequently detected in illicit drugs.

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Benzodiazepine Oncogenesis as Mediated via Diminished Restorative Sleep Effected Sympathoadrenal Activation

The valuable cohort contribution by Kao et al¹ associating narcotic zolpidem consumption with heightened iatrogenic malignancy risks would be considerably more compelling if accompanied by proposition of a distinct plausible pathophysiologic mechanism. The most favorably received mechanism would define associations between the physiologic effects of zolpidem that are common to other pharmacologic agents and diagnoses that effect similar intermediary stepwise events epidemiologically linked to oncogenesis.

Though newer benzodiazepine controlled substances are marketed as "non-benzodiazepines," zolpidem activates identical benzodiazepine sleep modulation γ -aminobutyric acid type A receptors as classic benzodiazepines,² enhancing superficial stage 1/2 sleep interval at the expense of restorative rapid eye movement and stage 3/4 deep slow wave sleep (SWS).^{2,3} Benzodiazepines thereby enhance sleep duration, but at the expense of

restorative sleep. Similarly, all benzodiazepines suppress afferent carotid body⁴ and medullary ventilatory centers, enhancing central sleep apnea perils.⁵ Nocturnally ingested opioids are also well characterized as enhancing sleep duration but suppressing SWS⁶ and inducing central sleep apnea,⁵ with potential oncogenesis.

A 22-year study of obstructive sleep apnea has suggested that malignant lesions are potentially mediated by hypoxemic angiogenesis.⁷ However, sleep apnea induced hypoxemia propagates awakenings, fragmenting SWS architecture,⁸ alternatively explaining reported epidemiologic findings. Polysomnographic SWS findings were unreported. In addition, the authors did not discuss decreased oncogenesis in SWS preserved, chronically iron-depleted anemic hypoxemic, non-apnea conditions bereft of carcinogen exposure.⁹

Further challenging the angiogenesis hypothesis, non-hypoxemic circadian sleep impaired shift work decreases melatonin, which effects parallel rapid eye movement and SWS duration decrements,¹⁰ diminishing sleep duration by 1 to 4 hours to compromise restorative sleep quality and concomitantly increase cancers.¹¹ In addition, without sleep apnea hypoxemia, 42,351 patients with sleep disorders with unknown extent of SWS deficit revealed a substantially elevated risk of cancer.¹²

Analogous to benzodiazepine and opioid impaired restorative SWS without decrement in overall sleep duration, experimentally laboratory simulated selectively fragmented SWS impairment without compromise of total sleep duration induced sympathoadrenal hyperactivity, increasing circulating cortisol and catecholamines⁸ as well as hyperglycemic dyshomeostasis.¹³

Impaired restorative SWS effects daytime cognitive impairment and neurobehavioral angiogenesis, with attendant augmentation of nocturnal sympathoadrenal hyperactivity,¹⁴ perpetuating and magnifying hyperglycemia.

The constant aberrant serologic hyperglycemic environment detrimentally compromises white cell optimal cancer scavenging immunosurveillance, facilitating unimpeded microscopic tumor growth to macroscopic tumor bulk. Clinically expressed immunosuppression facilitates oncogenesis, as witnessed in patients with diabetes, those with human immunodeficiency