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Editorial

Brazil's zolpidem crisis: structural lessons from the first wave of the US opioid epidemic

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This is a preliminary, unedited version of a manuscript that has been accepted for publication in the Brazilian Journal of Psychiatry. As a service to our readers, we are providing this early version of the manuscript. The manuscript will still undergo copyediting, typesetting, and review of the resulting proof before it is published in final form. The final version may present slight differences in relation to the present version.

Brazil's zolpidem crisis: structural lessons from the first wave of the US opioid epidemic

Running title: Brazil's zolpidem crisis

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Sales of zolpidem in Brazilian private pharmacies rose from approximately 1.03 million units dispensed in 2014 to 2.54 million in 2021, that is, 2021 dispensing reached approximately 246% of the 2014 level, corresponding to a relative increase of approximately 146%, while benzodiazepine sales remained stable before declining[1]. This divergence is consistent with a progressive shift away from benzodiazepines toward a medication widely perceived as carrying lower dependence risk, a perception that current evidence no longer supports. In 2024, the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária, ANVISA), the federal authority responsible for the regulation and surveillance of medicines, medical devices, food, cosmetics, and health-related products and services in Brazil, reclassified zolpidem to the B1 category of controlled psychotropic substances under Portaria SVS/MS nº 344/1998, which requires dispensing against an individually numbered blue prescription form (Notificação de Receita B) retained

by the pharmacy and valid for a limited number of days within the state of issue, a framework functionally analogous to Schedule IV controlled-substance regulation in the United States and to comparable scheduling systems elsewhere[2]. This was a necessary corrective, but it addresses only the most downstream element of a problem whose architecture runs considerably deeper.

The structural dynamics sustaining Brazil's zolpidem overprescription bear a disquieting resemblance to those that defined the first wave of the US opioid epidemic (1990s–2010), the iatrogenic phase that preceded heroin diversion and illicit fentanyl[3]. The resemblance is not pharmacological; it is architectural. We use the term "crisis" not to imply a mortality burden comparable to opioids, but to denote a preventable, iatrogenically reinforced pattern of widespread long-term prescribing, dependence risk, regulatory lag, and inadequate non-pharmacological treatment alternatives. In both cases, a newer agent was introduced under a narrative of superior safety, amplified through clinical and commercial framing as a safer alternative to existing options, and sustained by a widening gap between accumulating evidence of harm and clinical practice. In both, chronic prescriptions extended well beyond guideline-recommended durations, creating populations of physiologically dependent patients, while regulatory intervention arrived years after prescribing patterns had become culturally entrenched. We draw this parallel not to equate the magnitude of these crises, which differ profoundly in mortality and illicit market dynamics, but to underscore that these categories of systemic failure recur across drug classes with a regularity that should command attention.

The pharmacological differences are consequential. Opioid overdose is directly lethal; isolated zolpidem toxicity is rarely fatal. Cumulative opioid-involved deaths in the US exceed 800,000 since 1999[3]; no equivalent mortality signal exists for zolpidem in Brazil. Yet the morbidity burden is substantial and underrecognised. Zolpidem dependence produces tolerance, dose escalation, and withdrawal syndromes that may resemble benzodiazepine withdrawal, including severe cases. Associated harms include cognitive impairment (particularly among older adults), increased fracture and fall risk[6], motor vehicle accidents, and complex sleep-related behaviours, the last of which prompted a boxed-warning safety communication from the United States Food and Drug Administration in 2019[7]. In the US, overdose deaths involving Z-drugs tripled between 2000 and 2018[4]. Emerging evidence also links Z-drug exposure to elevated suicide-related outcomes[8,9], a finding of particular

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concern given that insomnia itself independently predicts suicidal behaviour[10], and coprescription with other CNS depressants, including opioids, benzodiazepines, and alcohol, substantially increases overdose lethality[4,7]. The absence of a conspicuous mortality signal should not be conflated with the absence of a crisis.

What distinguishes Brazil's current situation is that the problem has been identified while the window for preemptive action remains open. Capitalising on this requires a response calibrated to the realities of a dual healthcare system (Table 1). In the private sector, where specialist access is less constrained, cognitive behavioural therapy for insomnia (CBT-I) should be positioned as first-line treatment for chronic insomnia, consistent with the American College of Physicians clinical practice guideline[11] and the American Academy of Sleep Medicine clinical practice guideline on behavioural and psychological treatments for chronic insomnia in adults[12]. More recently, acceptance and commitment therapy has emerged as a safe and effective alternative, with randomised controlled trials conducted in Brazil[13]. Structured deprescribing protocols should become standard psychiatric practice, informed by the Brazilian Academy of Neurology clinical guideline on Z-drug abuse and dependence[5]. In the public system (Sistema Único de Saúde, SUS), where the scarcity of trained psychotherapists makes individual CBT-I delivery unrealistic at scale, a pragmatic, primary-care–level approach is needed, centred on brief, structured sleep-hygiene and stimulus-control counselling deliverable by primary care physicians, nurses, and community health workers in 5–10 minutes, supported by standardised patient handouts; explicit limitation of pharmacological treatment to short courses with planned reassessment; and referral to specialised services reserved for treatment-resistant or complex cases. Multicomponent CBT-I, when available, should be prioritised for these complex cases. Evidence-based digital CBT-I tools, once validated, culturally adapted, and made accessible to the Brazilian population, may extend reach but cannot replace face-to-face care for patients with limited digital literacy or unstable internet access. Integrating insomnia screening into routine chronic disease management would represent a low-cost, high-yield intervention.

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Table 1. Proposed differentiated action framework for addressing zolpidem overprescription in Brazil

Domain	Private healthcare	Recommended public-sector implementation pathway (SUS)
(1) First-line clinical treatment of chronic insomnia	Multicomponent CBT-I delivered by trained psychologists or psychiatrists as the initial intervention.	Pragmatic, primary care–level approach centred on (i) brief, structured sleep-hygiene and stimulus-control counselling deliverable by primary care physicians, nurses, and community health workers in 5–10 minutes, supported by standardised patient handouts; (ii) explicit limitation of pharmacological treatment to short courses with planned reassessment; and (iii) referral to specialised services reserved for treatment-resistant or complex cases. Multicomponent CBT-I, when available, should be prioritised for these complex cases. Evidence-based digital CBT-I tools, once validated, culturally adapted, and made accessible to the Brazilian population, may extend reach but cannot replace face-to-face care for patients with limited digital literacy or unstable internet access.
(2) Structured deprescribing	Standardised psychiatrist-led tapering protocols informed by the Brazilian Academy of Neurology Z-drug guideline; planned follow-up during taper; substitution of CBT-I when indicated.	Gradual tapering supervised within UBS/ESF teams, with referral pathways to specialised outpatient mental health services, CAPS, or CAPS-AD for severe withdrawal or complex presentations; tapering protocols adapted to medicines available through the SUS pharmaceutical assistance network.
(3) Prescriber education	Continuing medical education on Z-drug dependence potential and alternatives; updated specialty-society guidelines.	Short, accredited continuing-education modules on Z-drug pharmacology, dependence, and pragmatic non-pharmacological alternatives; case-discussion support at the point of prescription decision via existing teleconsultation channels; revision of undergraduate medical and residency curricula represents a

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Domain	Private healthcare	Recommended public-sector implementation pathway (SUS)
		longer-term complementary goal.
(4) Pharmacist-level interventions	Pharmacist-led screening for chronic dispensing trajectories at the point of dispensing; counselling on dependence risk and non-pharmacological alternatives; coordination with prescribers when long-duration use is identified.	Same, integrated, where applicable, into UBS pharmacy services and SUS pharmaceutical care (Assistência Farmacêutica) workflows; coordination with community pharmacies when dispensing patterns suggest long-duration use.
(5) Patient education (cross-cutting)	Plain-language information on dependence risk, complex sleep-related behaviours, fall and motor-vehicle accident risk, and the existence of non-pharmacological alternatives; shared decision-making prior to initiation; explicit expectation management during deprescribing, including the possibility of transient rebound insomnia and short-term withdrawal symptoms.	Same, delivered through primary care visits, community-pharmacy counselling, community health worker (ACS) home visits, and SUS public-health communications, with materials adapted to varying literacy levels.
(6) Regulatory framework (cross-cutting)	Initial prescriptions limited to 7–14 days with mandatory reassessment for renewal; CPF-linked integrated dispensing monitoring across all pharmacies, analogous in purpose to US Prescription Drug Monitoring Programs, paired with safeguards against undertreatment.	Phased regulatory roadmap: (i) immediate enforcement of existing B1 dispensing requirements; (ii) limitation of initial prescriptions to 7–14 days with mandatory clinical reassessment for renewal; (iii) medium-term development of CPF-linked dispensing data integration, analogous in purpose (not equivalence) to US PDMPs, with safeguards against undertreatment of patients with legitimate clinical need; (iv) longer-term creation of prescriber-facing dispensing-trajectory alerts. Each step requires distinct legal, technical, and financial investment.
(7) Surveillance (cross-cutting)	Integration of Z-drug monitoring into existing poisoning and overdose registries (e.g., the CIATox toxicological information network); prospective cohort studies quantifying dependence burden; tracking of Z-drug-	As a first-line measure feasible with existing data, periodic publication of state- and municipality-level Z-drug dispensing rates derived from SNGPC reports (the federal regulatory system that tracks

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Domain	Private healthcare	Recommended public-sector implementation pathway (SUS)
	associated suicide-related outcomes and complex sleep-related events.	entries and exits of controlled medicines from private pharmacies and drugstores), followed by inclusion of Z-drug–related adverse events in the CIATox toxicological information network. Longer-term integration with national SUS information systems (e.g., SINAN for notifiable adverse drug events; SIM for mortality with hypnotic involvement) would require dedicated indicator development.
(8) Special populations	Heightened caution and shorter prescribing windows for older adults, patients receiving concomitant CNS depressants (opioids, benzodiazepines, alcohol), and patients with substance use disorders; structured tapering and integrated addiction-medicine referral when indicated.	Shorter prescribing windows for older adults and patients with substance use disorders; integration with the CAPS-AD network for the latter, acknowledging that systematic gerontological pharmacovigilance within primary care remains a goal rather than an established capability.

Framework developed by the authors, integrating recommendations from the American College of Physicians clinical practice guideline on chronic insomnia disorder in adults[11], the American Academy of Sleep Medicine clinical practice guideline on behavioural and psychological treatments for chronic insomnia[12], and the Brazilian Academy of Neurology clinical guideline on Z-drug abuse and dependence[5], contextualised to the dual public–private architecture of the Brazilian healthcare system. The components listed describe recommended actions adapted to existing Brazilian healthcare infrastructure; with the exception of the 2024 regulatory reclassification of zolpidem to Category B1, many of the system-level interventions proposed here are not yet routinely or nationally implemented and would require coordinated investment, workforce training, policy development, and local adaptation for systematic deployment. ACS = Agentes Comunitários de Saúde (community health workers); CAPS = Centro de Atenção Psicossocial; CAPS-AD = Centro de Atenção Psicossocial – Álcool e Drogas; CBT-I = cognitive behavioural therapy for insomnia; CIATox = Centros de Informação e Assistência Toxicológica; CPF = Cadastro de Pessoas Físicas (Brazilian individual taxpayer identification number); eMulti = Equipes Multiprofissionais na Atenção Primária à Saúde (successor to the Núcleos Ampliados de Saúde da Família, NASF); ESF = Estratégia Saúde da Família; SIM = Sistema de Informação sobre Mortalidade; SINAN = Sistema de Informação de Agravos de Notificação; SNGPC = Sistema Nacional de Gerenciamento de Produtos Controlados; SUS = Sistema Único de Saúde; UBS = Unidade Básica de Saúde.

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Across both sectors, structural interventions are needed, and these are best conceived as a phased roadmap rather than a single set of actions. As an immediate step, the 2024 reclassification subjects zolpidem-containing medicines to the blue prescription form (Notificação de Receita B), strengthening prescription-level oversight; however, this form-based mechanism does not integrate dispensing across prescribers, pharmacies, or jurisdictions at the individual patient level. Consequently, Brazil still lacks a real-time, prescriber-facing, patient-level monitoring system analogous in purpose to US Prescription Drug Monitoring Programs (PDMPs); the SNGPC (Sistema Nacional de Gerenciamento de Produtos Controlados), the regulatory system that tracks entries and exits of controlled medicines from private pharmacies and drugstores, does not link prescriptions to individual patients in real time, allowing the same individual to obtain multiple zolpidem prescriptions from different prescribers undetected. In the medium term, a CPF-linked integrated dispensing database for all B1 substances could help identify overlapping prescriptions, high-dose use, and prolonged dispensing trajectories, although such monitoring should be implemented alongside expanded access to non-pharmacological treatment, deprescribing support, and safeguards against undertreatment of patients with legitimate clinical need; in the longer term, prescriber-facing dispensing-trajectory alerts could be developed. Each of these steps requires distinct legal, technical, and financial investment. Initial prescriptions should be limited to a few days with mandatory reassessment for renewal. Medical curricula must incorporate training on Z-drug dependence and non-pharmacological alternatives. Finally, epidemiological surveillance of Z-drug-related harms, currently absent, must be established by leveraging existing data – including periodic publication of state- and municipality-level Z-drug dispensing rates derived from SNGPC reports and inclusion of Z-drug–related adverse events in the CIATox toxicological information network – with longer-term integration into national notification (SINAN) and mortality (SIM) systems requiring dedicated indicator development.

The structural parallels between Brazil’s zolpidem trajectory and the first wave of the US opioid epidemic are not destiny; they are a diagnosis. They reveal how a false safety narrative, unchallenged by timely regulation and adequate clinical alternatives, entrenches overprescribing patterns that become progressively harder to reverse. Brazil has something the United States did not have in the late 1990s: a

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documented precedent and the self-awareness to act before entrenchment. The ANVISA reclassification was a necessary first step, but prescription control without investment in treatment infrastructure, prescriber education, individual-level monitoring, and active surveillance will prove insufficient. The evidence, the precedent, and the tools exist. The question is whether Brazil will use them in time.

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