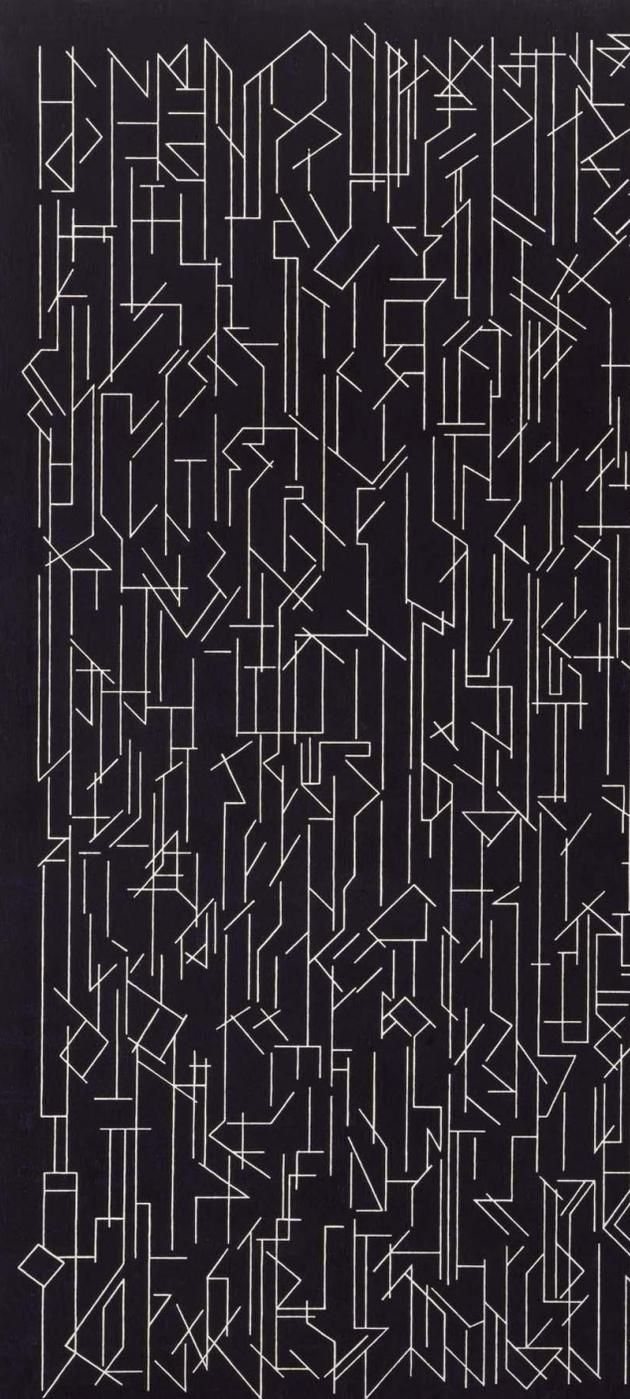


Z-Drugs Dependence: An Awakening Truth

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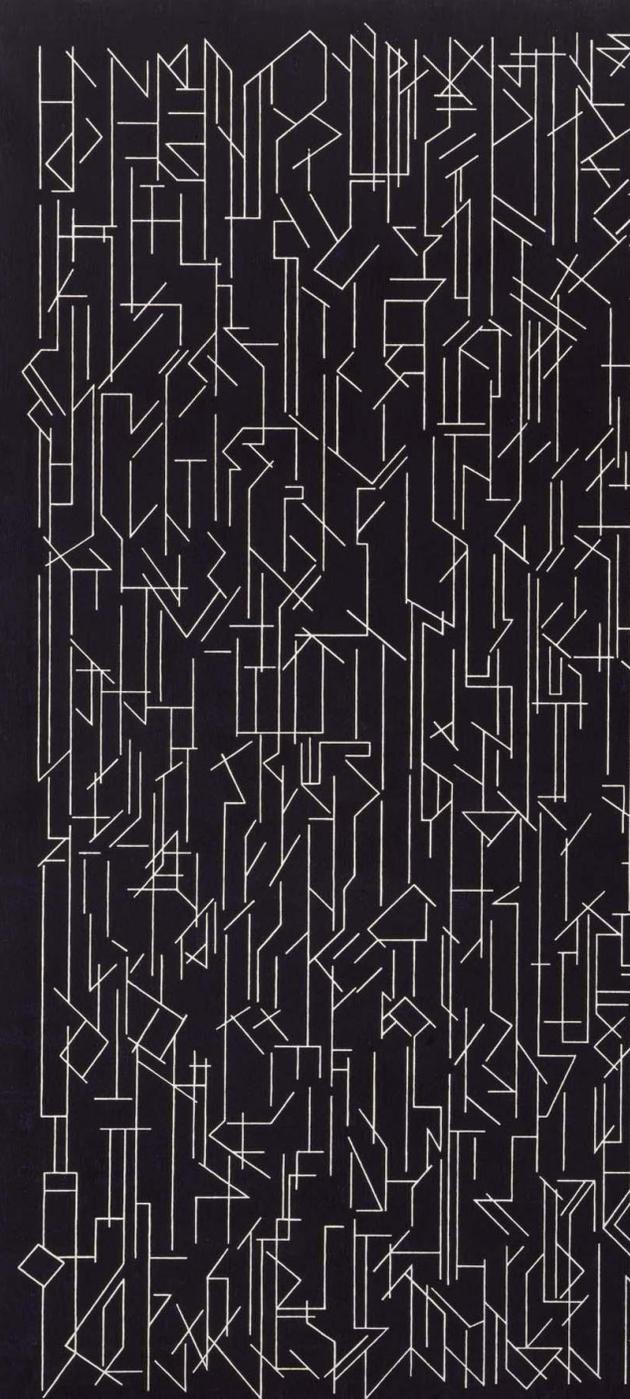
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BACKGROUND.

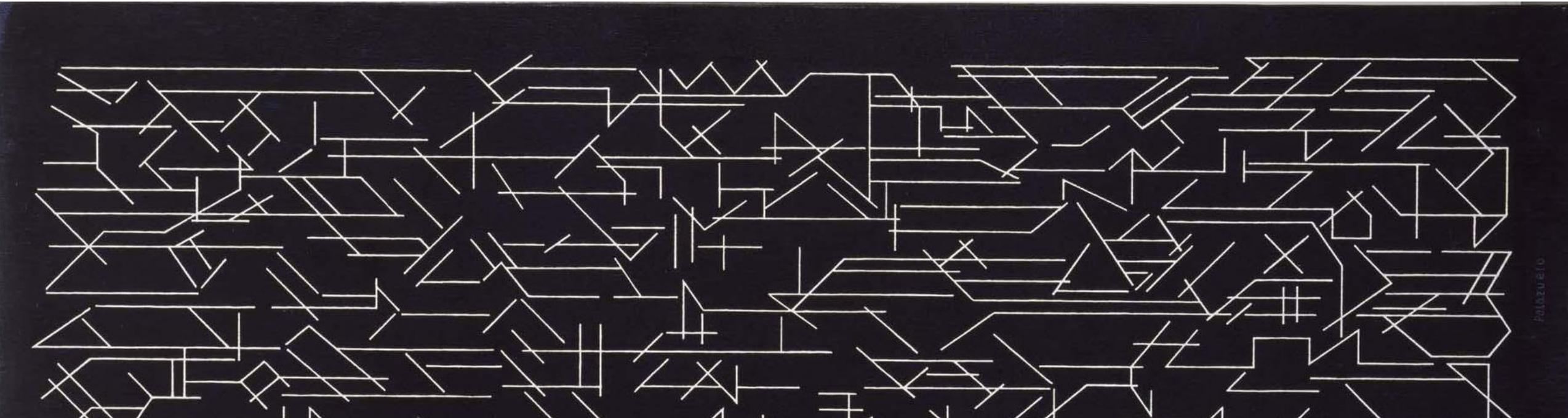
- > Z-drugs – zolpidem, zopiclone, zaleplon – **positive allosteric modulators for GABA_A receptors** (alpha1 subunit).
- > Initial trials and first clinical studies described them as great hypnotics and an **alternative to Benzodiazepines** (BZD) due to their safer pharmacological profiles: less side effects, complications, tolerance, **abuse and dependence**. (13) Early appraisal and a **sense of safety** with an increase in prescriptions. (6, 11, 13)
- > Growing **evidence of side effects** (e.g. morning drowsiness, odd behaviour) and complications (e.g. falls and bone fractures) **lead to new prescription guidelines**. (5, 13, 15) This rising awareness also led to a **steadiness/decrease in new prescriptions but an increase in long-term prescriptions**. (2, 3, 6)



What about misuse, abuse, addiction and dependence potential?

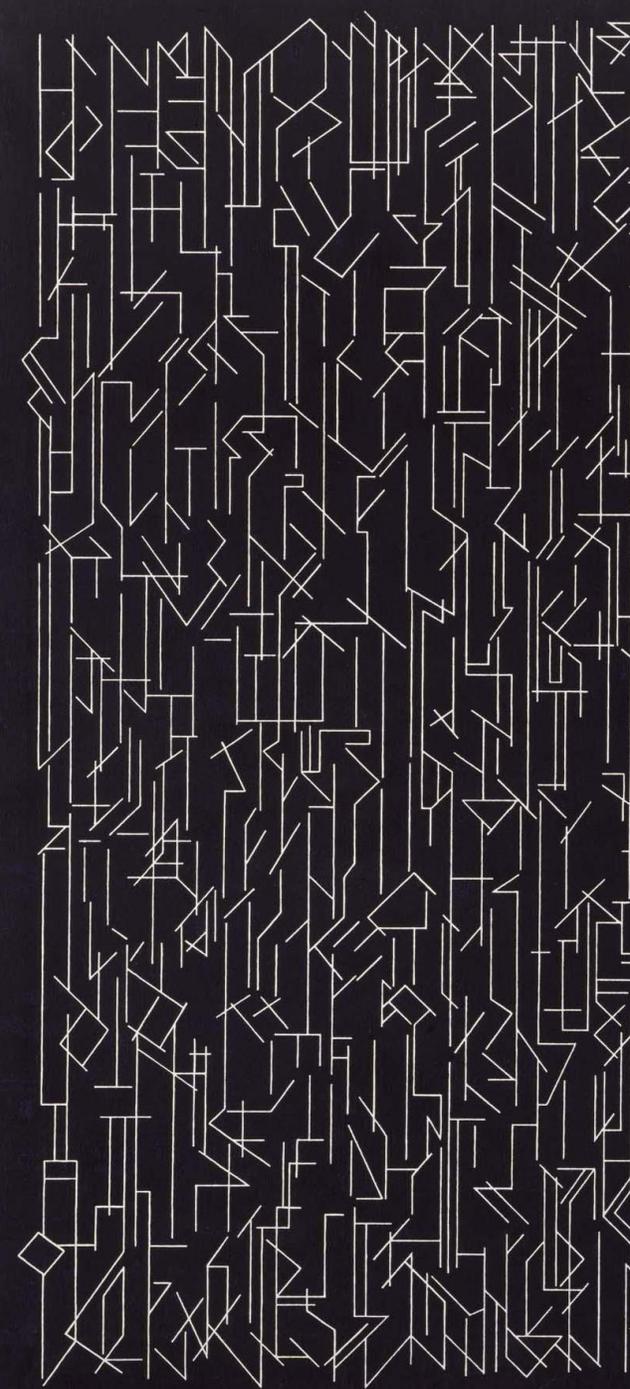
Objective: highlight relevant aspects concerning Z-drugs misuse and dependence known to date.

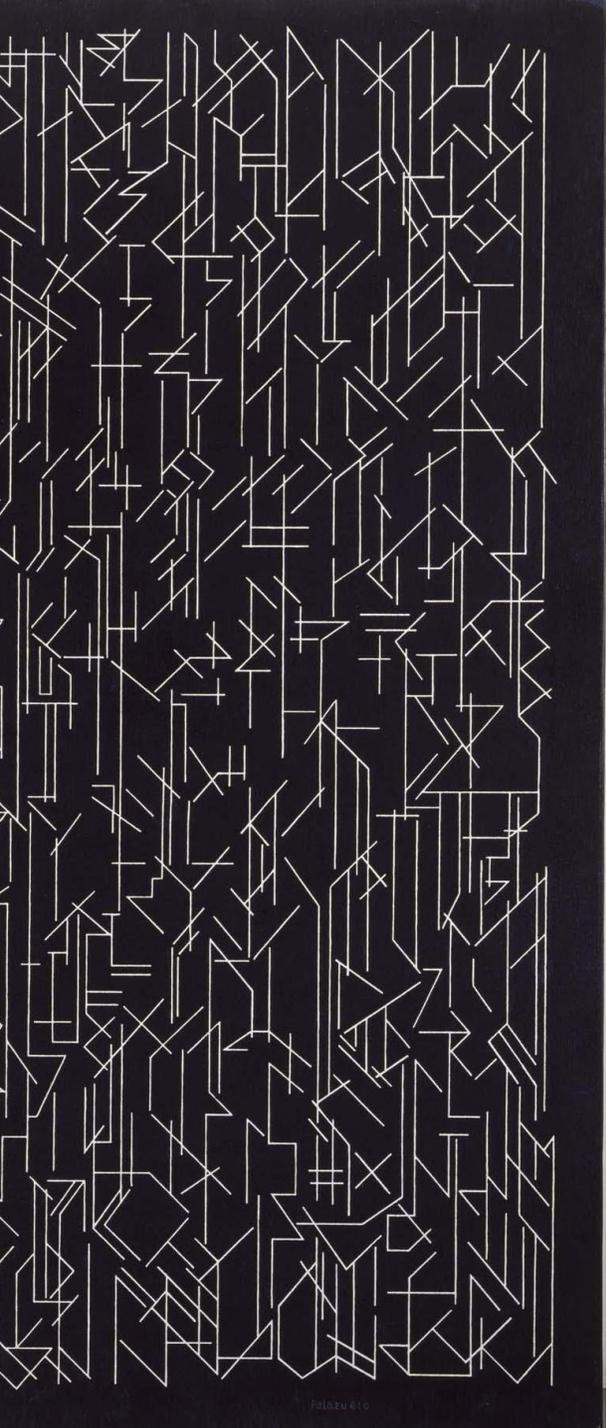
A search was conducted in PudMed, from which the relevant articles were selected and reviewed.



WHAT.

- > Abuse/misuse rates, as dependence and addiction rates, **are higher than initial studies show**. Although there's not an exact estimate, the number of case reports **keeps growing**. (8, 15)
- > Known estimates for misuse usually refer to either BZD or Z-drugs: in some studies, **rates are as high as half the population**. (17)
- > **For decades, doses consumed in misuse cases have been rising**: one study show they have doubled in reports from 2004 to 2011. (18)





WHO.

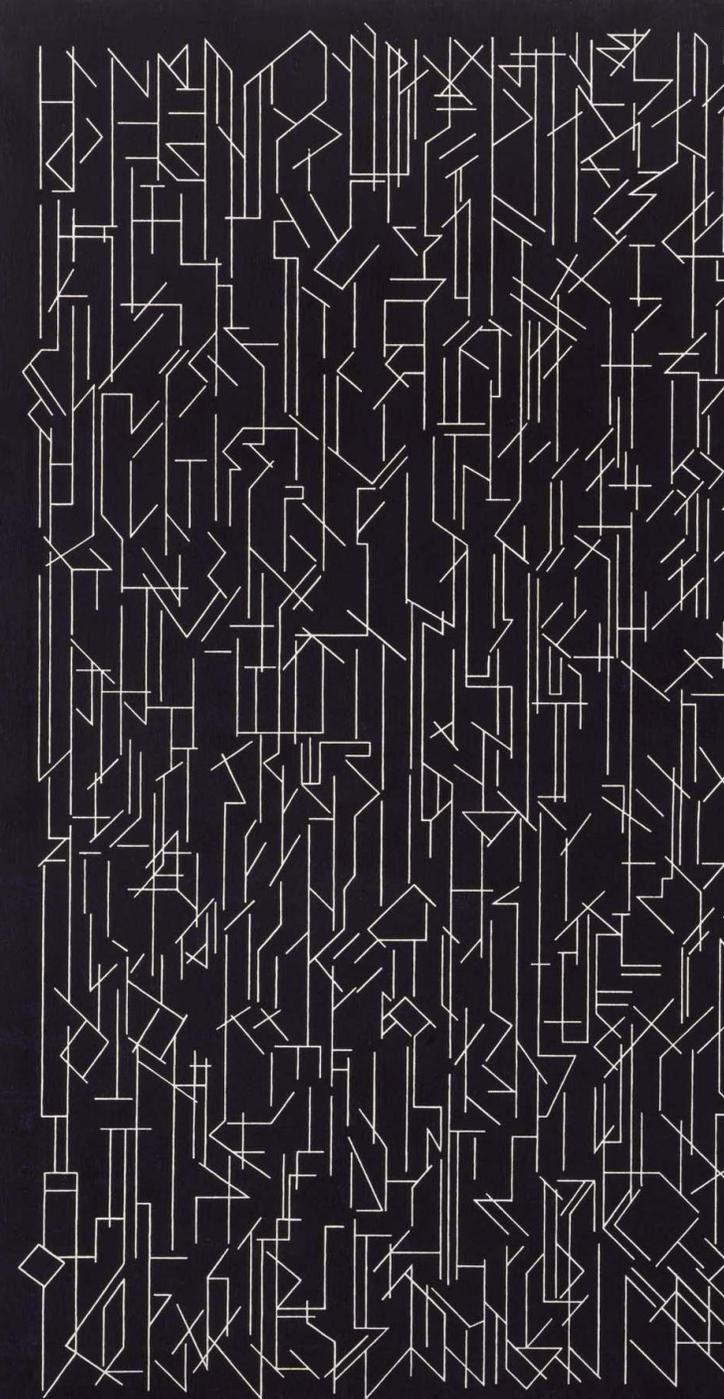
- > **Psychological stress and psychiatric history** are significantly associated with z-drugs dependence. (1, 4, 14, 17)
- > Patients who abuse z-drugs have significantly higher rates of **past use and use disorders of tranquilizers and other prescription drugs** (includ. BZDs). (1, 7, 13, 14, 17) This was also true for other drugs, and z-drugs are usually consumed in association with **other recreational drugs**. (15) In some studies, the use of z-hypnotics was associated with regular alcohol intake. (1, 4, 10, 13)
- > One study with patients attending care centres for drug addict patients showed that in 75 patients using z-drugs, **diagnosis of dependence was reported in 20 (27%) patients and abuse in 13 (18%)**. (18)
- > Z-drugs may be attractive to specific populations with misuse habits because they are **not typically monitored during drug treatment programs**. (13)
- > Importantly, **some studies outlined abuse, dependence and withdrawal syndrome in patients without evidence of previous abuse or psychiatric disorder**. (16)

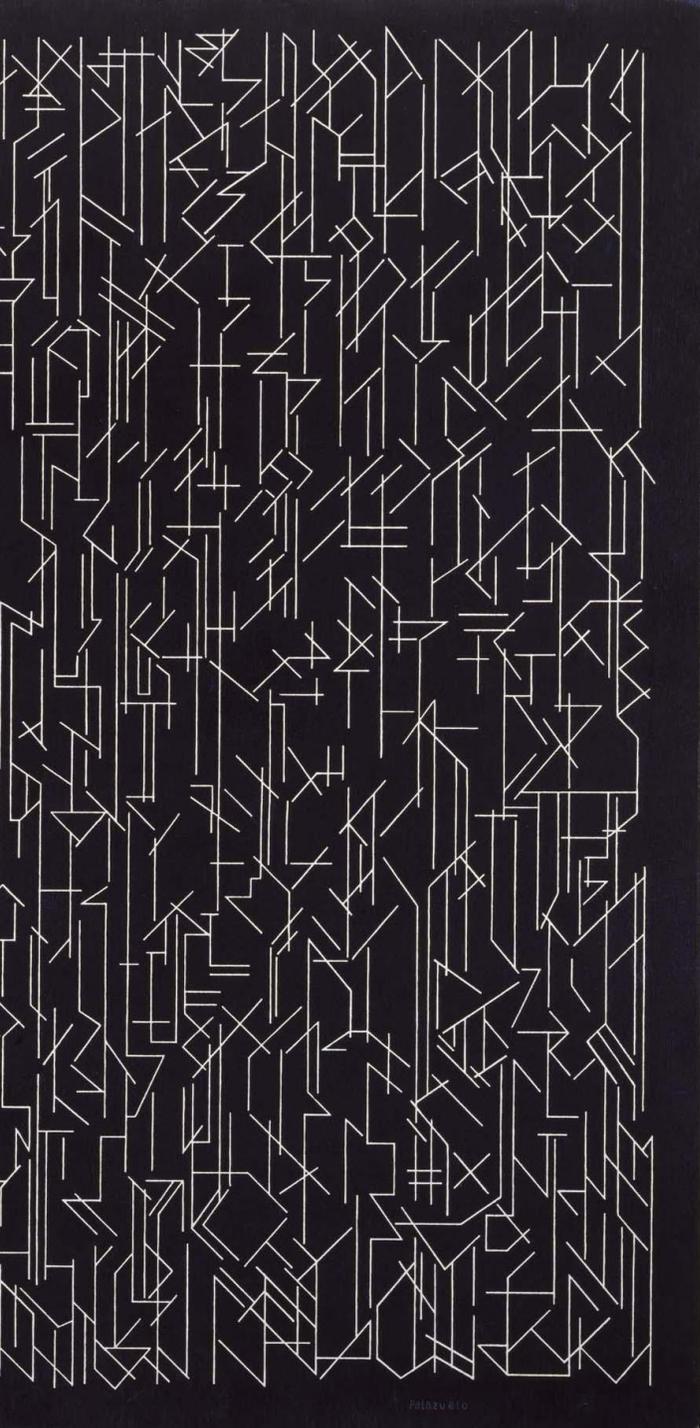
WHO.

Two big subsets of individuals misusing z-drugs have been identified in different studies:

> One including an **older** population with psychiatric comorbidities or other illness, originally medicated with z-drugs for **insomnia but who slowly develop tolerance, craving and withdrawal symptoms**, leading to increasing dosages and allowing for an unusual anxiolytic effect of supratherapeutic doses; this, in the end, **contributes to long-term usage**. (9, 13, 15, 16) Interestingly, one study suggests practitioners are more tolerant about long-term usage with older patients.

> The other group includes **younger people, ingesting large Z-drug dosages in combination** with other recreational compounds and through **unusual intake modalities** (e.g. injected or inhaled) to facilitate **paradoxical reactions achievable with high doses** - e.g. “euphoria”, “feelings of well being”, “being able to cope with everyday” or hallucinations. (12, 13, 15, 16) **These patients usually develop dependence and increase doses rapidly** (16). This pattern of use, with the search for positive psychic effects, seems to be growing for the last decades (18).





HOW.

- > The low incidence of cases reported compared to the widespread use of z-drugs suggests **a continued unawareness** of their abuse potential leading to its underreport. (16). Long-term treatment is little reported, and a certain level of overdosing appears to be accepted by medical professionals. (16) When patients talked about practitioners role, the **lack of adequate information about risks and the lack appropriate support for safe withdrawal** where also noted. (12)
- > The measures implemented in several countries in order to try to control misuse (e.g. adding information about dependence risk to the summary of drug characteristics) **seem to have been ineffective.** (18)
- > An UK survey from 2014 showed that around 70% of the z-drug misuser respondents obtained the medication from a single source, while the rest 30% respondents obtained it from multiple sources. **Divergent prescriptions are known to contribute to problematic patterns of use** (8, 10)
- > With numbers growing for years, **Z-drugs are now present in 20% of the forged or falsified prescriptions in France;** zolpidem appears in 5% of all notifications, making it **the number one drug appearing in forged prescriptions** (16, 18). Other sources may include friends and/or family, internet sellers, street dealers and importing from abroad. (8)

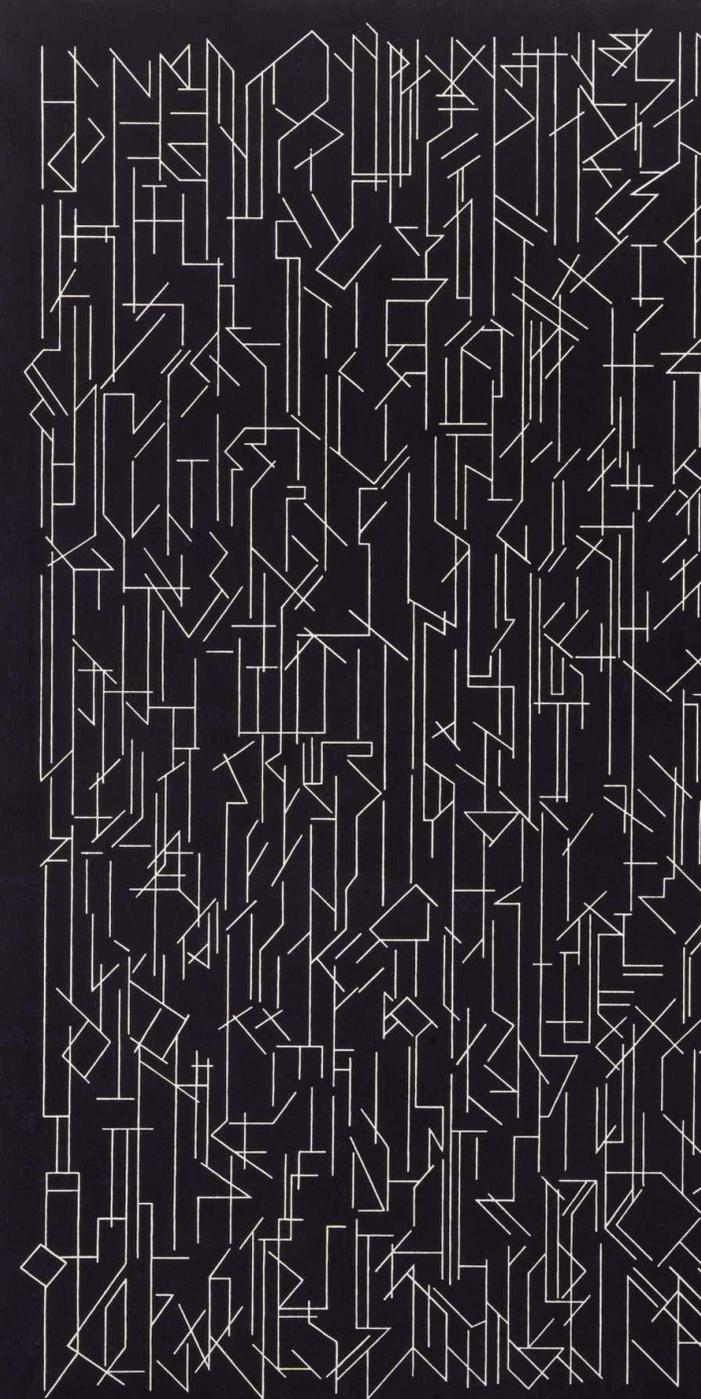
CONCLUSIONS.

> **Z-drugs dependence and misuse is clearly more prevalent and relevant than assumed earlier.** Meanwhile, available studies allow for and provide some suggestions on important actions to address z-drug misuse:

> Practitioners should provide adequate information and withdrawal plans to patients using z-drugs. Also, they must be aware of and explore signs of misuse and dependence syndromes, like patient's characteristics, patients requesting high doses of medication or mentions to paradoxical effects. (17)

> National and international health policy makers should target general public (as opposed only health professionals) in their strategies to address z-drugs misuse. (18)

> Nevertheless, while it is already possible to understand some issues related to z-drug misuse, future studies are needed not only to clarify its epidemiological and clinical aspects but also to allow us to understand the different dimensions of the problem in order to adopt adequate health measures.

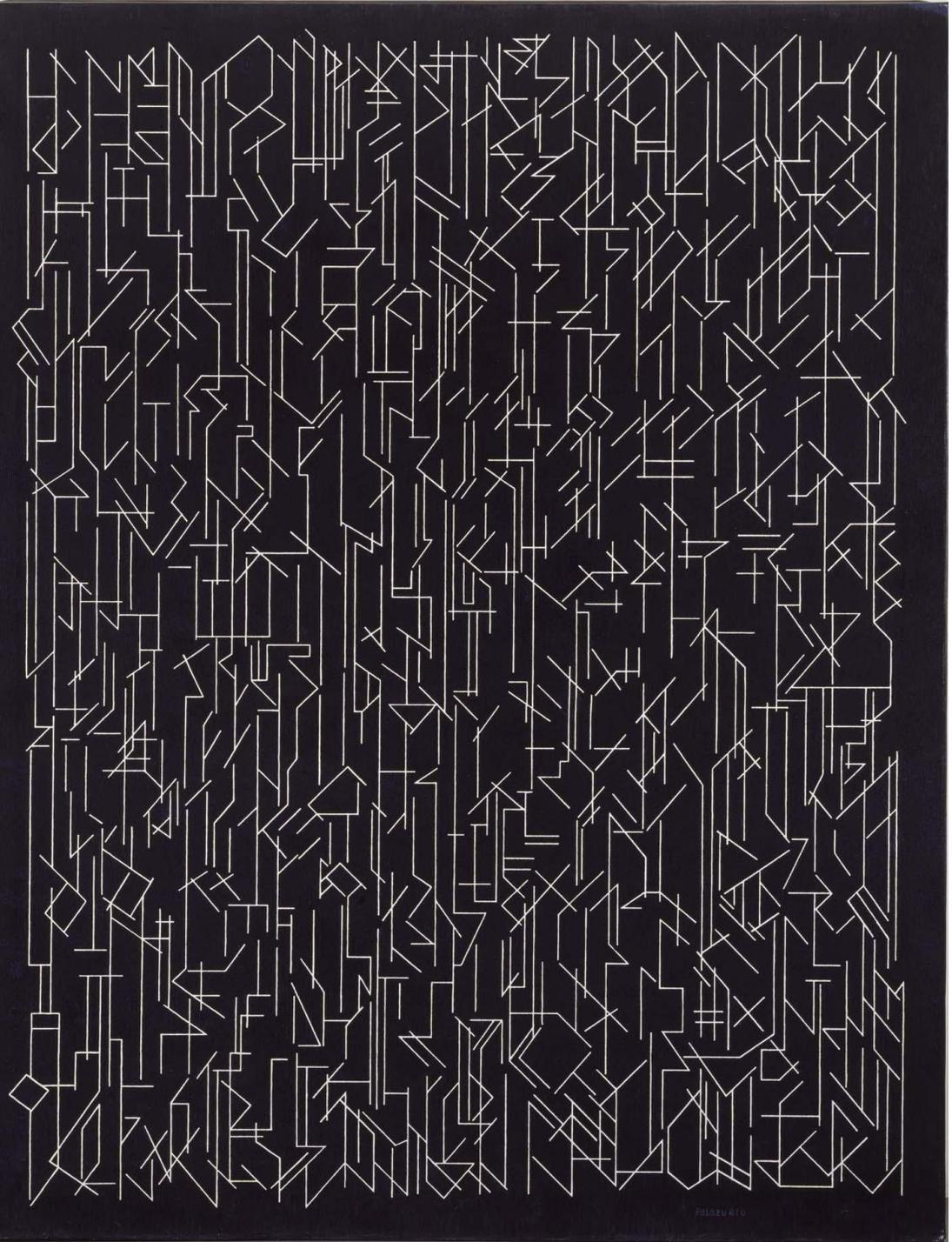


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THANK YOU!

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