REVIEW OF ABSTINENCE SYNDROME: A COMPREHENSIVE ANALYSIS OF CURRENT PRACTICES AND RECOMMENDATIONS

ABSTRACT:

Alcohol use disorder (AUD) is frequently accompanied with the diverse and sometimes fatal consequence of alcohol withdrawal syndrome (AWS). Many patients with AUD may develop AWS during their ED stay, and AUD is one of the top causes of death worldwide. The epidemiology, pathophysiology, and treatment of AWS and AUD in an emergency situation are summed up in this review. The influence of AWS on the therapy of ED is highlighted, along with its temporal course. Symptom-triggered benzodiazepine administration is still the most often used treatment for AWS after a diagnosis, however it might not be suitable for patients who are about to be discharged or have serious medical or mental comorbidities. In these situations, ED physicians could think about using shorter barbiturate courses or other regimens built on cutting-edge anticonvulsants. For clinical practice, specific treatment procedures are described. Lastly, in addition to managing acute patients' AWS, emergency physicians also need to provide the groundwork for effective AUD therapy. A strategy for the patient with AUD's disposition is offered.

KEYWORDS:

Phenobarbital, gabapentin, alcohol use disorder, benzodiazepines, and alcohol withdrawal syndrome

INTRODUCTION:

Alcoholism is one of the most common psychiatric problems, although only after a serious condition. Up to 10% of people with alcohol dependence and 50% of people with alcohol addiction exhibit symptoms. In [2] Frequent and excessive alcohol intake leads to the development of alcohol tolerance and physical dependency. The main cause of the withdrawal syndrome is the central nervous system's hyperexcitable reaction to the lack of alcohol. [3–6] Gamma-aminobutyric acid (GABA) and glutamate are two excitatory and inhibitory neurotransmitters that are out of balance in alcohol

withdrawal syndrome (AWS), a potentially fatal medical disease. [7–8] The diagnostic criteria for alcoholism are met by around 27% of people between the ages of 18 and 64.[9]

Alcohol Use Disorder (AUD) can lead to Alcohol Withdrawal Syndrome (AWS), a potentially fatal consequence that affects many patients in emergency departments (EDs) [10]. Inpatient hospitalization and the use of critical care services are more common when alcohol withdrawal occurs in the emergency room. Over half of those with symptoms of alcohol withdrawal are middle-class, employed people, which makes diagnosing them difficult [11]. Many physiological and psychological symptoms, including as insomnia, shaking, autonomic hyper-reactivity, anxiety, depression, restlessness, fidgetiness, seizures, hallucinations, and, in severe instances, delirium tremens (DT), are indicative of Alcohol Withdrawal Syndrome (AWS) [12]. Alcohol Use Disorders, or AUDs, are the third most common risk factor for illness and impairment worldwide. Surprisingly, AUDs are thought to be responsible for 2.3–3.3 million more fatalities per year than HIV and TB combined [13–15].

According to the American Academy of Family Physicians, withdrawal symptoms can appear anywhere between six and twelve hours after quitting. These symptoms include headache, sweating, lack of appetite, mind and hand tremors, and sleep problems. b) 12–48 hours after cessation seizures that include withdrawal symptoms, tonic-clonic seizures all over, and hallucinations c) Delirium tremens, elevated blood pressure, heart rate, and fever 48–72 hours after discontinuation. [16] An estimated 5% of the worldwide population has alcohol use disorder (AUD) each year, affecting around 18% of the total population.[17] Alcoholics with cirrhosis have a high mortality rate when they consume alcohol regularly. [18] Obesity, hypertension, obstructive sleep apnea, and left ventricular dysfunction are some of the risk factors for atrial fibrillation that are associated with alcohol use. [19] AWS is a spectrum of neurophysiological symptoms that vary in severity according to the amount of alcohol consumed. [20,21]

STAGES OF ALCOHOL WITHDRAWAL SYNDROME

- **6 Hours Sober**-Most withdrawal symptoms start: headache, anxiety, mood swings, nausea, nausea and so on.
- **12-24 Hours Sober**- Symptoms continue and can escalate to hallucinations and seizures.
- **24-48 Hours Sober**- Symptoms persists. On average symptoms peak after 24 hours for mild withdrawal.
- **48-72 Hours Sober**-Delerium Tremens (DT) can start which include increased heart rate, temperature, and seizure. DTs can be fatal.
- **72+Hours Sober**-Symptoms and peak gradually subside after 5 days. Symptoms may persists for upto one month.

Stage-1

Uncomplicated withdrawal- Tachycardia, hypertension, and hyperthermia are some of the symptoms of mild to severe autonomic hyperactivity that may also be included in it. [22,23,24]

Stage-2

Alcohol hallucinosis - It affects 2-8% of people who use alcohol excessively and chronically, particularly those who started drinking when they were 17 years old or younger. [25]

Stage-3

Alcohol withdrawal seizures- It usually presents as widespread tonic-clonic seizures and affects 5–10% of those with active Alcohol Withdrawal Syndrome (AWS). [26]

Stage-4

Alcohol withdrawal delirium- An alternative name for this syndrome is tremendous delirium (DT), and 3-5% of instances of AWS are associated with DT patients. [27]

BIOMARKERS

Numerous research works have investigated possible signs of an approaching severe AWS. Examining medical history and testing for biomarkers are the two main techniques for determining high risk. A history of a similar event appears to be the most accurate predictor of a DT or seizure episode occurrence. [28,29,30,31]

The first patient examination may simply screen for clinical indications such as raised heart rate, temperature, and systolic blood pressure, even though these measures have a low predictive value for determining which AWS patients are more likely to develop DT. In cases where a patient's level of awareness is compromised, test indicators may bolster the clinical suspicion of a AUD. [28,29,32]

Table-1 SEVERE ALCOHOL WITHDRAWAL: A DISTINCTIVE DIAGNOSIS

Distinct diagnosis	Comments
Hyponatremia	The causes are poor oral intake, uremia, and dehydration; these conditions usually result in hypoactive delirium.
Hepatic encephalopathy	Common symptoms of severe liver illness, especially cirrhosis, include hematemesis, melena, ascites, icterus, jaundice, sleep-wake reversal, and flapping tremor.
Pneumonia	Before quitting alcohol usage, some people may have symptoms including fever, coughing, low arterial blood oxygen saturation, and pre-cessation delirium, which might indicate a complicated interaction of elements impacting their health.
Psychosis	The presence of persistent hallucinations or delusions without any clouding of the sensorium is a noteworthy clinical characteristic that can be found in several mental illnesses.
Encephalitis/Meningitis	Meningeal symptoms, specific neurological impairments, fever, and abnormalities found in MRI and cerebrospinal fluid (CSF) studies can all be indicators of different neurological disorders.
Lithium intoxication	Past medical history including mental disorders, drug abuse, fever, diarrhoea, and use of diuretics or NSAIDs.
Subacute encephalopathy with seizures in AUD	People may have simple or complicated partial seizures with reversible motor impairments a few days after stopping drinking. While MRI may indicate reversible T2-weighted flare hyperintensities, focal slowness and periodic lateralized discharges are frequently seen in EEG data.
Head injury	Unconsciousness, bleeding from the nose or ears, pinpoint pupils, and localized neurological impairments.
Atropine/Tricyclic intoxication	Hyperthermia, desiccation, and dilated pupils
Thyrotoxicosis	Past thyroid conditions such as thyromegaly, exophthalmos, and lagophthalmos
Antidepressant intoxication	SSRI use; constipation, myoclonus, anxiety, convulsions, and altered sensory perception

COMORBIDITIES

- Alcohol withdrawal delirium is a condition that cannot be treated with benzodiazepines , thus it is important to differentiate it from hepatic encephalopathy.
- Because they are metabolized by the kidneys, intermediate-acting benzodiazepines like oxazepam and lorazepam are thought to be safer to take.
- When using benzodiazepines, care should be taken if there are symptoms of end-stage liver disease, such as ascites, variceal bleeding, or hepatic encephalopathy.
- Furthermore, in cases of hepatorenal syndrome, further caution is necessary. For the treatment of mild to moderate AWS, gabapentin and baclofen are suitable substitutes.
- Thiamine supplements at high doses are imperative for all patients experiencing severe AWS to prevent the onset of Wernicke's encephalopathy.[33]

NEUROIMAGING

- Since status epilepticus (SE) and first-onset seizures are often linked with concurrent risk factors more than 50%, neuroimaging is recommended to rule out other neurological ailments in these individuals."
- The most common MRI abnormalities associated with seizures are cerebral hyperintensities and hyperperfusion, along with a low apparent diffusion coefficient in CT regions with decreased attenuation, effacement of sulci, and absent grey-white differentiation.[34]

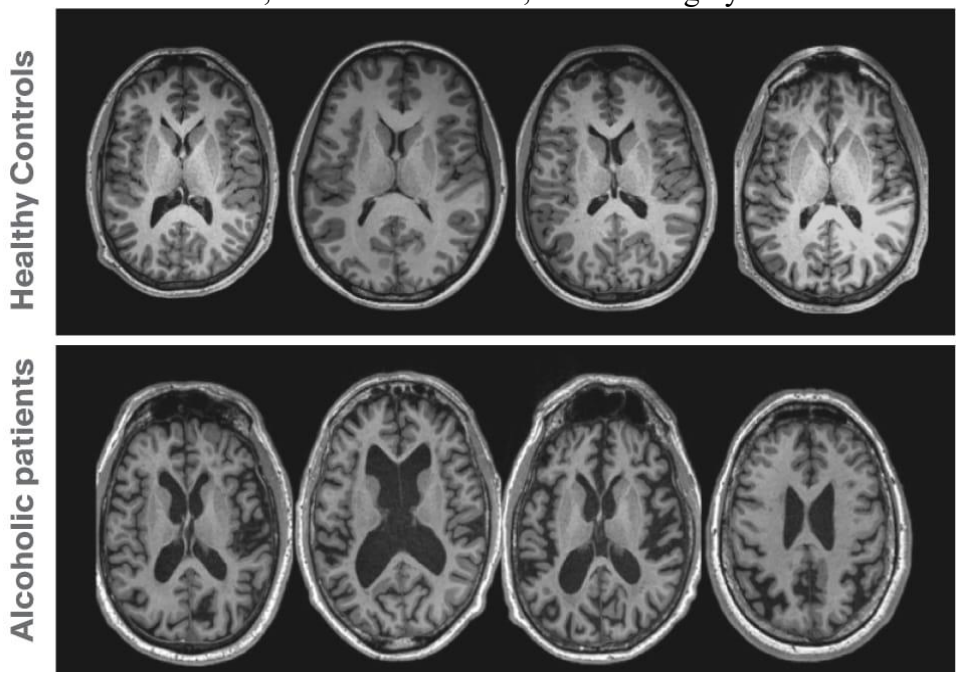


Fig-1 Neuroimaging

Table-2 Radiographic Markers in Patients' Brain Images Associated with Alcohol-Related Syndromes

Disease Associated with Alcoholism	Abbrevation	Principal Area(s) Targeted	Subsequent Areas of Focus	Rate of Alcoholism Prevalence (Percent)
Marchiafava Bignami Disease	MBD	Corpus callosum	Cortex	<0.002
Alcohol-Related Dementia	ARD	Frontal cortex		3-24
Alcoholic Cerebellar Degeneration	ACD	Cerebellum		0.4-42
Wernicke's Encephalopathy	WE	Mammillary bodies, periaqueductal grey matter, dorsal medulla, tectal plates, olivary bodies, pons, tissue surrounding 3rd ventricle		12–18
Korsakoff's Syndrome	KS	Mammillary bodies, hippocampus, thalamus, orbitofrontal cortices	Cerebellum, pons	12-15
Central Pontine Myelinolysis	CPM	Pons	Basal ganglia, thalamus, cerebral grey-white matter	<0.5

ELECTROENCEPHALOGRAM

- Brain activity may be recorded using an electroencephalogram, or EEG.
- In order to detect the electrical impulses generated by the brain, tiny sensors are affixed to the scalp during this painless examination

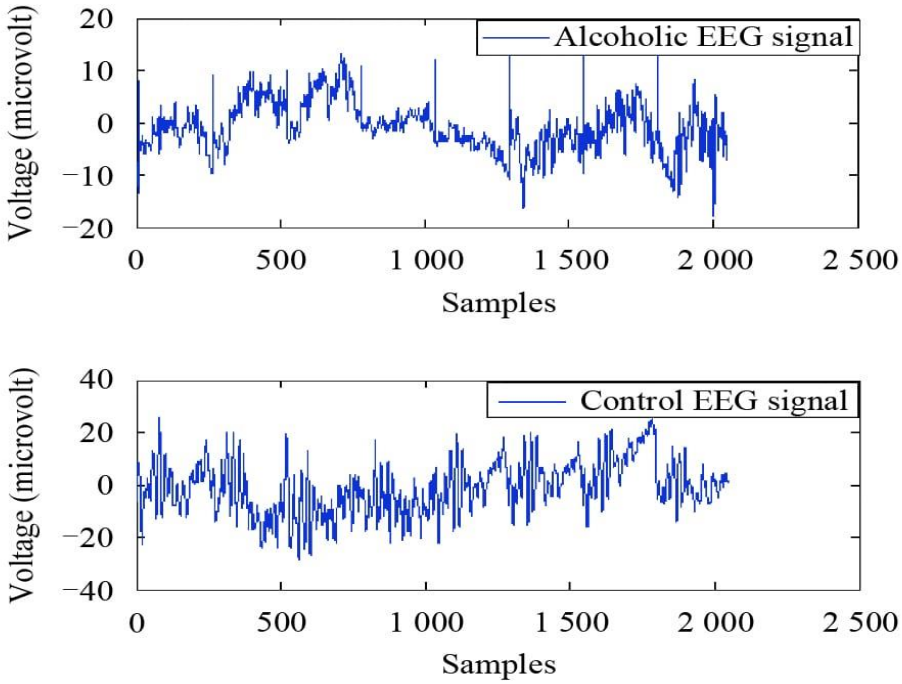


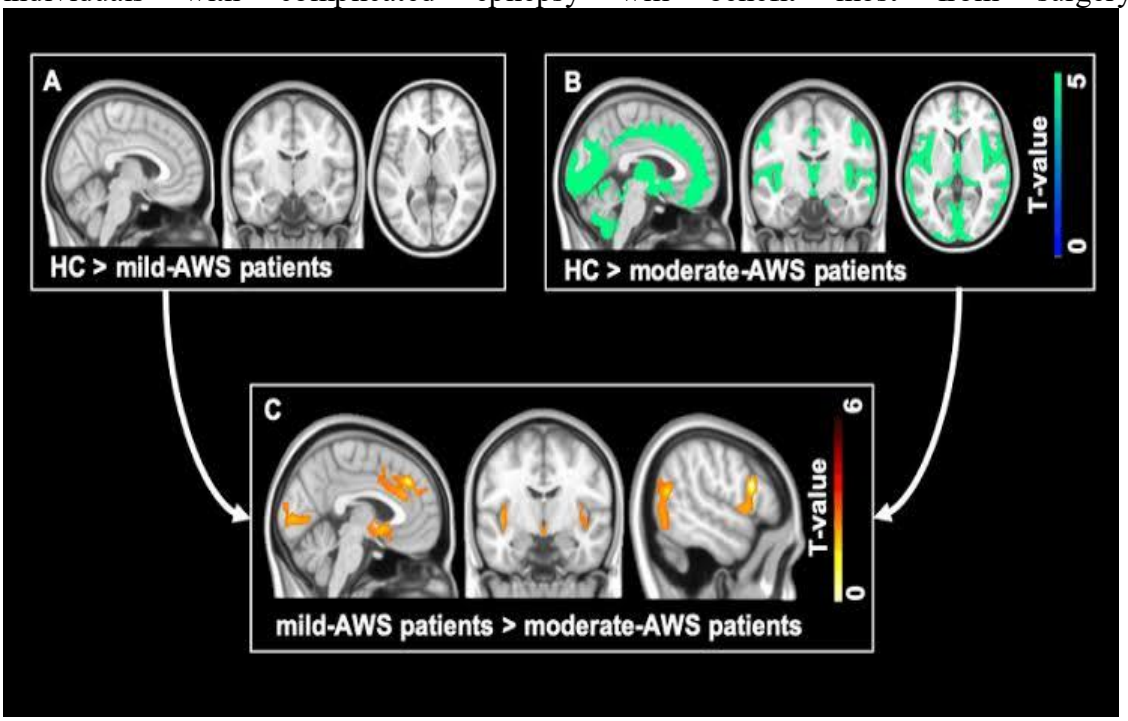
Fig-2 Electroencephalogram signals

- The primary purpose of an EEG is to diagnose and study epilepsy, a condition that causes recurring seizures [35]

Types of EEG

- **Regular EEG**: An EEG recording normally lasts 20 to 40 minutes. Another option is to use a flashing light to see how your brain reacts to this.
- **Ambulatory EEG**: This type of EEG monitors brain activity during the day and at night for a period of one or more days. A small, wearable, clippable EEG recorder will be attached to the electrodes.
- **Sleep EEG**: An electroencephalogram is recorded while you are asleep. When a standard EEG is insufficient to diagnose sleep issues, it can be utilized as a test.
- **Video telemetry**: Also referred to as video EEG, video telemetry is a special kind of EEG in which you are being recorded while being videotaped. This may help to clarify further information on how your brain works.

- **Invasive EEG monitoring**: Although rare, this kind of EEG can be used to assess whether individuals with complicated epilepsy will benefit most from surgery.[36]



TARGETS OF THE TREATMENT

1. "To facilitate a gradual and safe taper off the drug or drugs of dependence, supporting the patient in achieving a drug-free status."
2. "To offer a compassionate withdrawal process, preserving the patient's dignity during their journey to recovery."
3. "To prepare the patient for ongoing therapy and treatment for their alcohol or drug dependency."[37]

ASSISTIVE CARE

- **Comorbid medical conditions**-If they exist, they should be addressed. Oral or intravenous fluids should be used to treat metabolic disturbances. It must be a serene, tranquil, and unstimulating atmosphere. [38]
- **Dietary Supplements**-It is recommended to experimentally supply thiamine (vitamin B1) in order to avoid Wernicke's encephalopathy (WE) and Korsakoff's psychosis. There are differences in protocols for thiamine dose and delivery routes. Institutions and rules of the medical profession, with dosages ranging from 100 mg of thiamine up to 200–500 mg per eight hours for a standard IV fluid infusion 72 hours at least if WE is detected. [39,40]

AWS-SPECIFIC THERAPEUTICS

- **Table-3 Benzodiazepines [42]**

Drugs used	Available Route of Dose	Comparative Equivalent Strength	Action Commencement (Following Oral Administration)	Peak Blood Levels (Hours)	Half life (hrs)	Duration of Action	Metabolism
Midazolam	PO, IM ,IV	2	Rapid	Oral: 0.2-2.5 IM:0.5-12	2-7	Short	Hepatic, gut

Clorazepate	PO,IM	7.5	Rapid	0.5-2	48	Short	Hepatic
Lorazepam	PO,IM,IV	1	Intermediate	Oral:2 IM:<3	12-18	Short to Medium	Hepatic
Diazepam	PO, IM,IV	5	Rapid	Oral:0.25-2.5 IM:1 IV:0.01	30-60	long	Hepatic
Chlordiazep oxide	PO	10	Intermediate	0.5-2	24-48	long	Hepatic

- **Anticonvulsants**

Long-term heavy drinkers may be affected by the prolonged abstinence syndrome, which implies that they depend on alcohol for stress relief, reward experiences, and a sense of normalcy [41]. It can take many months or even years of sobriety to reverse the negative effects of alcohol on the brain. It is believed that NBACs efficiently treat the hallmarks of protracted abstinence syndrome, such as impaired hedonic function, stress reactivity, and cravings. NBACs may lessen the symptoms of prolonged abstinence syndrome by improving glutamatergic and GABAergic neurotransmission in the ventral striatum and related neurocircuitry. After a patient attains sobriety, anticonvulsants can support healing processes and equilibrium. It's possible that interactions between glutamate and dopamine are what keep addiction going [42].

Glutamatergic efferents originating from the hippocampus, amygdala, and prefrontal cortex innervate neurons located in the nucleus accumbens shell and ventral tegmental region. This process amplifies dopaminergic neurotransmission in these crucial circuits linked to the reward system.[43]

- **Antiepileptics**

With a fixed or tapering regimen spanning 5–9 days and daily dosages of 800 mg, CBZ showed good tolerance and successfully reduced withdrawal symptoms. Nevertheless, obstacles including inadequate enrollment, postponed pharmacological administration, limited sample size, and incorrect dosage impede a definitive assessment of CBZ's function in averting seizures or delirium tremens (DT), and its relative effectiveness in comparison to benzodiazepines is still up for debate [44,45]. Levetiracetam's (LEV) exact mode of action in AWS is still unknown because it does not appear to have any affinity for either GABAergic or glutamatergic receptors. Nevertheless, the treatment of AWS with LEV appears promising; the available data indicate a steady and quick improvement in clinical outcomes. Studies are still being done to find out more about its applicability in treating AWS. [46,47]

2- Alpha Adrenoceptor Agonists and – betablockers

Blood pressure and heart rate are lowered by centrally acting α2-adrenoceptor agonists like clonidine and lofexidine, as well as β-blockers like propranolol and atenolol, which help to regulate withdrawal-induced sympathetic activity. While some research studies [48,49] indicate the usefulness of these drugs in reducing certain withdrawal symptoms, other studies have not demonstrated any appreciable advantage over a placebo in managing symptoms including nausea, anxiety, and agitation. Crucially, there is now no proof that these drugs are effective in treating DT or averting withdrawal symptoms. [50]

Barbiturates

Research conducted on small or uncontrolled populations has shown promise in the treatment of withdrawal with barbital, phenobarbital, and tetraborate [51,52]. In acute withdrawal scenarios,

their smaller tolerance margin strongly suggests against their usage, and their efficacy does not considerably outperform that of benzodiazepines.[53]

Nitrous Oxide (NOx)

Gillman and Ojutkangas [54] found that 62% of 500 Finnish patients needed just one nitrous oxide treatment and recovered totally from withdrawal symptoms within 60 minutes [55], in contrast to the usual 4- to 5-day recovery period associated with benzodiazepine therapy. In South Africa, almost 7,000 people received nitrous oxide therapy for alcohol withdrawal during a ten-year period [56]. The study team located in South Africa suggests that nitrous oxide injection might be used as a screening method to identify withdrawal patients that need to be treated further with medicine to keep symptoms from dangerously getting worse [57]. To fully understand the potential of nitrous oxide as a monotherapy or polytherapy, however, extensive controlled research studies are required.

THERAPY

Relapse therapy: Relapses happen gradually, as you should be aware. Weeks or perhaps months pass before someone starts using drugs or alcohol. The major objectives of treatment are to help patients recognize the early warning indicators of relapse and to help them build coping abilities so they may stop relapses before they happen. [58]

➢ **Stages of Relapse-**

• Emotional relapse

• Mental relapse

• Physical relapse

Alcohol Rehabilitation-The process of treating alcohol dependency using a combination of medical and psychological therapy is known as alcohol rehabilitation. In particular, alcohol rehab is a program or therapy utilized when someone who has misused or overindulged in alcohol stops using it with the intention of staying sober for good. Detoxification, rehabilitation, and sobriety maintenance are typically included in the treatment process. Reference [59] Recognizing the issue and getting treatment for alcoholism are the most crucial steps in the process. Among the early warning indicators are: [60].

- Isolation from friends and family
- Signs of irritation and irritability
- Making excuses to consume more alcohol
- Choosing alcohol over other obligations in life
- Feeling hungover when not drinking

Various ways for de-addiction;

- Psychoeducation
- Detoxification
- Intensive psychotherapy

Cognitive Behavioural Therapy-Today, a lot of people utilize it to treat addiction. CBT helps people with substance use disorders (SUDs) discover links between their ideas, feelings, and behaviours and

raises understanding of how these factors affect recovery. Patients can overcome alcoholism and drug addiction with the use of CBT by:

• Offering self-help methods to improve their emotions;

• Assisting in the dismissal of incorrect ideas and anxieties that cause substance abuse

• imparting knowledge on effective communication [61]

Electroconvulsive therapy-It is an effective therapy for a variety of acute mental and neuropsychiatric disorders and entails the therapeutic generation of seizures utilizing pulsed electrical stimulation. [62,63,64] The actual delirium, agitation, and possible long-term impacts on cognition are recognized side effects of ECT therapy. [65]

DISCUSSION

The primary reason for choosing this topic was to educate readers about the serious health effects of abruptly quitting alcohol consumption. The primary benefit is that people with alcoholism can be treated at various phases using pharmacological and non-pharmacological interventions. The drawback is that abruptly quitting alcohol use might cause insanity and even death.

CONCLUSION

By this project we conclude that anything taking in excess dose may leads to organ damage and at last death. So before taking alcohol may sure that ready for all consequences related to it.

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