QEEG and Neurofeedback Training for the Treatment of Substance Use Disorders: A Randomized Controlled Trial

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1. Relevance relative to the call for proposals

Substance use disorders (SUD) is considered one of the major public health concerns of our time, with high degree of comorbidity and far-reaching individual and societal implications. The dark figures are high, as only a small percentage of those affected seek help in treatment facilities, but it is assumed that between 10 and 20% of the population will experience problems related to excessive drug use in the course of their lives [1]. This makes SUD one of our most prevalent psychiatric conditions, compromising physical and psychological health and resulting in impairment in cognition, social relationships and quality of life (QoL), at high cost for society.

Of those who do seek treatment, relapse trajectories are discouraging. Some sources suggest that twelve-month relapse rates following cessation attempts from various classes of substance use can be more than 80% [2], implying that for the majority of those who enter traditional psychosocial or medication-based models of treatment relapses to drug use is common. In other words: the treatment of the disorder is as exceedingly complicated as is the disorder itself. A patient with a SUD typically requires comprehensive and life-long care across the different levels of service providers, from primary care to the specialist health care services, and case management for these individuals can be resource-intensive and complex. A systemic view of recovery is warranted, an interdisciplinary and integrative approach which aims to improve the physiological, psychological and social aspects of the disorder. New approaches to treatment, either new, stand-alone modalities or in conjunction with other therapies, are therefore constantly being sought.

2. Aspects relating to the research project

Background and status of knowledge
Traditionally, the dominant focus in addiction treatment has been on psychosocial approaches such as cognitive behavioral treatment, motivational interviewing, contingency management, 12-step programs, and pharmacological programs [3]. However, a growing awareness of the role of neurobiology in the development and maintenance of SUD [3, 4], has led to increasingly more international research interest being invested in efforts to develop and incorporate neuropsychological intervention methods into existing treatment paradigms [4, 5].

Through the use of modern brain imaging techniques such as quantitative electroencephalography methods (QEEG), in conjunction with low-resolution electromagnetic tomography (LORETA) or functional magnetic resonance imaging (fMRI), researchers have revealed that acute and chronic drug abuse can result in significant alteration of a person's brain activity [4, 6]. For instance, electroencephalography (EEG) investigations of patients with alcoholism have documented that even after prolonged periods of abstinence, they seem to have lower levels of alpha and theta waves and an excess of fast beta brain waves [7], making it difficult for them to relax. Following alcohol intake, however, the levels of alpha and theta brainwaves increase to normal levels. Such findings have led researchers to postulate that these individuals inadvertently use alcohol as a way of down-regulating their brainwave patterns to achieve the desired relaxed mental state. Conversely, psychostimulants can be used to "up-regulate" patterns which are associated with negative emotional states, such as depression. Thus, for the SUD patient, drug use can be a way of artificially normalizing these dysfunctional brain wave patterns.

Modern theories of cortical plasticity foster promise that such disturbed information processing can be reversible [8, 9]. One way of influencing brain activity directly is through EEG biofeedback. Also known as neurofeedback (NF), the method was first popularized for the treatment of alcohol dependence by the works of Eugene Peniston [10-12], and has been employed in the treatment of SUD for more than three decades. NF is a method aimed at reorganizing and normalizing brain wave patterns. Through electrodes placed on the scalp, oscillatory activity from the cortex is recorded and played back to the individual in the form of visual, auditive, and/or tactile stimuli, enabling shaping of the brain activity towards more functional patterns [13]. The aim of the NF training is to enable the

individual to develop skills for self-regulation of cortical activity. Because negative emotional states can trigger the urge to use drugs to achieve this regulation [2], neurofeedback can potentially prevent relapses through its calming effect on the central nervous system.

Peniston's encouraging outcome results in the eighties generated substantial interest in the addiction field, and efforts were made to replicate these findings. Several other studies using the Peniston protocol and its modifications reported cases with positive clinical effects, however, studies utilized primarily naturalistic design, sample sizes were small, description of methods insufficient and only few of these studies were published in mainstream peer-reviewed journals [14]. Consequently, the spread of the method has been slow, and it has not been applied systematically in addiction treatment. A recent review concluded that "Based on published clinical studies and employing efficacy criteria adapted by the Association for Applied Psychophysiology and Biofeedback and the International Society for Neurofeedback and Research, alpha theta training – either alone for alcoholism or in combination with beta training for stimulant and mixed substance abuse and combined with residential treatment programs, is probably efficacious" [14]. Since then, compiling empirical evidence, using alpha rhythms as well as other EEG band ranges, has demonstrated its efficacy for various forms of substance use disorders [15]. However, despite this growing evidence of its applicability, the method remains largely obscure and under-used in clinical applications for this patient population in Norway. To our knowledge, the addiction unit at the Clinic for Psychiatry and Addiction Medicine at Sørlandet Hospital is at present the only clinic nationwide applying the method systematically.

When neurofeedback was introduced and implemented as an adjunct treatment in our out-patient addiction clinic in 2011, many patients reported positive effects on a variety of comorbid symptomatology, and the retention rate for those who received the treatment was also significantly higher than the norm for this patient group. These observations were confirmed in a pilot study conducted at the clinic in 2012, in which the treatment was also rated positively by the patients [16]. Furthermore, data from subsequently admitted patients, measured by the same tools as in the pilot, have shown generally the same trajectory. These findings have spurred a motivation to conduct a larger, randomized controlled study to further investigate the role of NF in the treatment of SUD, this time with focus on its add-on effects to the treatment as usual (TAU) regime. Recognizing the high cost of treatment failure for society as large, as well as the high emotional cost for the individual, we wish to investigate whether the physiological effects of the treatment will help elicit positive emotional states which can strengthen coping behavior and aid patients in their efforts to become and remain abstinent. Thus, we believe that NF can play an important role in a relapse prevention paradigm and that its contribution can be captured with global patient-reported outcome measures such as well-being and QoL.

The current research proposal departs from previous studies in four important areas:

1. One of the challenges with a technology-driven intervention method such as NF is that research often lags behind the rapid technological development. Whereas most of the studies to date have utilized NF treatment protocols based on measuring subsets of the EEG activity, divided into band rangebandrange frequencies in the 4-30 Hz specter (such as Theta, Alpha, Beta rhythms), current clinical interest in some milieus has shifted to slow cortical potentials (SCP). SCPs are slow, event-related, direct-current shifts in the EEG, originating from the large cell assemblies in the upper cortical layer in the midline of the brain [17]. Newer software and hardware technologies have made it possible to isolate and process even slower bandwidths, so-called infra-low frequency training (ILF), i.e. frequencies below 0.1 Hz. This particular form of NF training seems to have the potential to influence the brain's resting state networks, which is thought to have a central role in underpinning overall brain function [18]. ILF training can thus be said to target core regulatory function of the central nervous system, rather than remediating specific deficits or diagnoses. This can explain the claimed wide applicability of the method across diagnoses and symptom categories. However, although favorably received in some clinical communities, the empirical support for the claims for ILF training is as of yet virtually non-existent. It is therefore important to fill this

apparent gap in the literature.

2. This study is among the few in the addiction treatment field that has QoL as its main outcome measure. The rationale behind this choice of outcome is that improvement of QoL can be viewed as an overarching aim of addiction treatment, a generic expression of the patient's global functioning and well-being. A high QoL has been found to correlate with positive affect, and can thus help maintain the motivation to stay sober. Nevertheless, in previous studies QoL is rarely assessed; reduction in substance use has been given main focus. If living without substance use is to be the goal for the SUD patient, this aim will simply not be perceived as ''worth'' striving towards if it is not associated with improved well-being in at least some facets of life. Consequently, patients may lose motivation and interest in their rehabilitative process [19].

3. Accordingly, the theoretical framework for this study will be to use NF as a strategy and potential tool in relapse prevention. Negative emotional states, such as anger, anxiety, depression, frustration, and restlessness are associated with higher rate of relapse to drug use [20]. By closely monitoring these variables throughout the project, we will be able to assess whether NF has a potential add-on effect on the patient's ability to cope with such negative emotions and the ensuing drug urge and cravings.

4. The proposed design has a stronger user involvement than previous research efforts in the field. User representatives with personal experience with NF will take an active part in the intervention and have regular dialogue meetings with participants, allowing informal exchanges about the method (e.g., possible effects and side-effects). We expect this element of the study to potentially boost the effect of the intervention. This way of boosting effects of other interventions has recently become a recommended strategy in the addiction treatment field [21].

Approaches, hypotheses, and choice of method

The overall aim of the study is to acquire more knowledge about the effectiveness of NF in the treatment of substance use disorders in general, specifically in relation to its effect on physical and psychological distress (e.g. sleep disturbances, anxiety symptoms etc.), and subsequently on its ability to improve QoL and prevent relapse. An RCT study will be undertaken to examine whether neurofeedback (NF) + treatment as usual (TAU) compared to TAU only can increase the QoL of patients with a SUD in the short and long term. We hypothesized that, compared to the TAU condition the NF + TAU condition would result in higher QoL at the end of treatment as well as at a 3- and 12-month follow-up. Included in our QoL assessment measure is perceived functioning in important areas such as work and social relations.

Our secondary outcome hypothesis is that the NF+TAU condition will result in better substance use outcomes as well as improvement in sleep quality, psychological distress, and symptoms of anxiety and depression at the end of treatment and at follow-up compared to controls. Drop-out rates will also be compared for the two groups, controlling for baseline demographic and severity variables.

In addition to the RCT, the project group will write up on an extended naturalistic cohort study initiated after the previous pilot, and investigate this cohort in relation to similar aims as described above.

Inclusion criteria

Patients with a substance use disorder referred to outpatient addiction treatment, aged >18 of both genders.

Exclusion criteria
Severe psychiatric disorders (e.g. psychosis) that have not been stabilized with e.g., medication (assessed as a part of the clinical process at the clinic). Severe cognitive impairment or language problems (inability to converse for interviews).

Experimental design
The proposed experimental study will have a two-group pre-post design with an intervention group (NF+TAU) and a control group (TAU). Participants will include patients referred to outpatient addiction treatment at two clinics within Sørlandet Hospital HF, in Kristiansand and in Arendal. Because regular attendance is desirable for participation in the project, certain clinical selection criteria will apply, but this will be handled not by the project group itself, rather it will reflect ordinary practice within the present clinical setting. Thus, patients are thought to be clinically eligible to the NF condition after having achieved an initial level of stabile attendance at the clinic. This is congruent with the study's focus on relapse prevention.

Patients meeting the criteria for inclusion will be informed about the project and given the opportunity to participate. After providing written, informed consent, those patients who choose to participate will be randomly assigned to either NF training + TAU, or TAU alone. The allocation will be determined through notes prepared in sealed envelopes by an external researcher based on a block randomization design. As a part of the NF+TAU condition, participants will be invited to an informal dialogue session within a month of starting the intervention, in which a user representative will be available to answer potential questions and share individual experience concerning the treatment. The TAU participants will receive standard psychotherapeutic treatment, chosen according to individual needs and therapist preference.

The intervention will consist of 20 sessions of symptom-based NF tailored to the individual patient. Training will be conducted using the Othmer method of NF from EEGinfo, comprising bipolar, infra-low frequency training, with the inclusion of synchrony and alfa-/theta training as needed.

All participants will complete the inventory described below at the outset. The instruments are chosen for their ability to measure internal states associated with a risk of triggering urges and cravings leading to drug use. Cognitive function is assessed because impairment in this domain is associated with poorer treatment outcomes, including decreased treatment retention in SUD patients [22]. QEEG data will be recorded prior to and after the 5 months intervention period. These data will be analyzed by our cooperating partner at Norwegian University of Science and Technology (NTNU) to identify possible biomarkers for addiction, and to study the neurophysiological effects of neurofeedback.

Instruments
In addition to basic demographics and the Mini International Neuropsychiatric Interview (M.I.N.I.) to confirm the SUD diagnosis [23], the inventory includes the items and scales below:

Primary outcome
- Quality of life, measured with
  - QoL-10, a 10-item questionnaire which rates the patient's subjective experience of life quality. The respondents are asked to rate their physical and psychological health as well as the quality of their relationships on five-point Likert scales. The scale also includes a subscale about perceived functioning in areas such as work, sexual and social relations [24].

Secondary outcomes
- Perceived functioning/well-being:
  - Outcome Rating Scale (ORS), a visual analogue scale consisting of four subscales measuring the patient's perceived functioning in the personal, interpersonal and social domains, in addition to a general measure of his or her perceived QoL. The respondents are asked to rate their perceived functioning in these areas from very low to very high on a 10 cm, unmarked horizontal line [25]. This scale was included to corroborate on the measurement of perceived functioning in

the QoL-10 functioning subscale and to be used in the repeated measuring of perceived functioning to assess trajectories of change (see below).

- Negative affect:
  - Mental distress will be measured with the Symptom Check List-10 (SCL-10). This scale is a 10-item index with a four-point response scale that maps anxiety and depression. It is an abbreviated version based on the more comprehensive SCL-90, and has been shown to be valid indicators of psychological distress. The corresponding cut-off point to the conventional 1.0 for SCL-90 is 1.85 [26, 27].
  - Restlessness and trepidation, measured with a visual analogue scale (VAS) on which the respondents are asked to rate their level of uneasiness from "none" to "very high" on a 10 cm, unmarked horizontal line [28, 29].

- Substance use:
  - Measured by selected questions from the European version of the Addiction Severity Index (EuropASI), a multi-dimensional interview used to measure a variety of aspects related to substance use [30].
  - Measured with two visual analogue scales (VAS), one for alcohol consumption and one for drug use, on which the respondents are asked to rate their intake in the last week by inserting a mark on a 10 cm, unmarked horizontal line [28, 29].
  - Perceived severity of substance use: As the study includes persons with both alcohol and drug dependence, we will also include a short, overall substance use severity measure at baseline; the Survey of Readiness for AA Participation (SYRAAP) severity subscale [31].

- Physiological variables:
  - Sleep quality, measured with a visual analogue scale (VAS) on which the respondents are asked to rate their sleep quality from "worst perceivable" to "best perceivable" on a 10 cm, unmarked horizontal line [28, 29].

- Cognitive function:
  - Measured with the Montreal Cognitive Assessment (MoCA), a brief screening instrument sensitive to mild cognitive impairment. The scale samples behavior across 14 performance tasks that engage multiple cognitive domains including attention, language, visuospatial, executive, and memory. Total possible score is 30 points, and a score of 26 or greater is classified as within normal range, that is, without evidence of cognitive impairment [22].
  - Measured with the QIK test – a continuous performance test devised to yield a reliable pre-post measure on attentional variables. It is a go/no-go challenge test, known as a choice reaction time test. It measures speed, accuracy and consistency and compares data to norms.

- To assess the *trajectories of change* in the NF-TAU condition, a simple computer-based screening test will be administered weekly to each participant during the project period, measuring: a) alcohol and drug use, b) sleep quality, c) restlessness and trepidation and d) perceived functioning (ORS). These VAS scales have been described above.

The participants will be reassessed after treatment and at a 3- and 12- month follow-up period. Research assistants (RAs) blinded to the patient's condition assignment will conduct the follow-up interviews. Efforts will also be made to examine non-completers. Respondents will be reimbursed NOK 250 ($30) for completing the follow-up interviews.

Sample size calculation

Sample size calculation is based on a previous study of a similar population where patients had a mean QoL score at 0.57 (SD 0.17) [32]. A minimal clinical relevant improvement and between group difference is considered to be 0.10 [33]. A sample size of 40 in each group has an 80% power to detect a 0.10 mean difference between groups with a significance level (alpha) of 0.05 (two-tailed). The power calculation was carried out with StatMate ver. 2.0 (GraphPad Software, Inc., San Diego, CA, US). We expect a 20% attrition rate at follow-up, thus, 50 patients will be needed in each group.

Statistics
Baseline variables will be reported with descriptive statistics. Difference between randomized groups on primary outcomes will be assessed with Student's t-test. Secondary outcome will be assessed with appropriate tests, e.g., the weekly repeated measures will be analyzed with generalized estimating equation (GEE) to test for differences between groups.

3. The project plan, project management, organization and cooperation

Project group:
- Principle investigator and PhD supervisor: John-Kåre Vederhus PhD, Addiction Unit (ARA), Sørlandet Hospital HF (SSHF)
- Assistant supervisor: Professor Thomas Clausen MD/PhD: ARA, SSHF and University of Oslo
- Statistical supervisor: Are Hugo Pripp PhD: Oslo Centre of Biostatistics and Epidemiology, Oslo University Hospital
- User representative: Ariel Khavari
- Clinical neurofeedback specialist, Karin Gabrielsen, MSc, ARA, SSHF

Advisory board:
The advisory board consists of national and international specialists on neurofeedback and QEEG [34, 35]. In addition, we cooperate with a community based researcher who is our link to the local municipality [36].
- Antonio Martins-Mourao, PhD, Clinical Director, London Scientific Neurotherapy
- Stig Hollup, Associate Professor, NTNU, Trondheim
- Finn Normann Thoresen, MD, outpatient clinic for social medicine, Østfold hospital
- Eirik Abildsnes, MD/PhD, Research advisor, Kristiansand Municipality

The specialists have commented on the project description and will participate in writing up on articles. In addition, Dr. Martins-Mourao will supervise and train clinicians for the QEEG procedures and Professor Hollup will be directly involved in interpretation of the QEEG results.

Existing research infrastructure
The Clinic for Psychiatry and Addiction Medicine (KPA), Sørlandet Hospital, has a large research portfolio. There are currently ten ongoing PhD research fellowships. Statisticians at Oslo University Hospital, has supervised previous projects at the site of the current study.

The proposed clinical study is being planned by the Research Department at ARA, Sørlandet Hospital. ARA is a subunit of KPA and has been carrying out addiction research since 1987. In the beginning, this was mainly naturalistic outcome research, and later intervention studies, randomized controlled trials, and registry studies were added to the portfolio [37-39]. A research unit was established in 2001 and currently comprises a research leader (MD/PhD), two senior researchers and two research fellows. Thomas Clausen MD, PhD from the Norwegian Center for Addiction Research (University of Oslo, UiO) acts as a research supervisor. Four PhDs at ARA have graduated via UiO or the University of Bergen (UiB). The studies of two of these students were supported by grants from the Norwegian Research Council; these studies were completed in 2012/2013 [40, 41]. ARA is also taking part in other ongoing cooperative projects with national collaborators and local community based research projects, as encouraged by the health authorities. Previous collaborations include international cooperation, e.g., with US researchers [39, 42].

Feasibility
Since neurofeedback was introduced to clinical practice at the Addiction Unit at Sørlandet Hospital HF (ARA) in 2011, a total of 10 clinicians have undergone training by EEGinfo in the Othmer method. Five of these are currently using it actively in their clinical work, constituting an experienced team of therapists who are skilled in data collection. The pilot study conducted at the unit in 2011/2012 [16] provided valuable experience on which to build the proposed study. The main focus of the pilot was SUD and comorbid PTSD, and since then outcome data from the treatment sessions have

been systematically collected for clinical use using similar instruments to those proposed here. Thus, data collection for the study will follow already established routines at the clinic. Based on the pilot study and practice at the clinic, the number of participants needed for this study is realistically achievable during the course of the planned two-year inclusion period.

Project time frame

- April 2017: Apply for relevant permissions (e.g., ethical approval). Clinical trial registration. Apply for funding.
- Autumn 2017: After ethical approval has been obtained, implement the experimental study in lieu of the clinical practice at ARA. Data collection.
- Autumn 2017: Find qualified PhD candidate as soon as funding is secured. Qualified graduates (with master's degrees) are currently doing clinical work at ARA. They are expected to apply for the position and will be able to start at relatively short notice.
- January 2018 to December 2019: Continue the experimental study and data collection
- Spring 2018. Start writing the first article based on the naturalistic cohort consecutively admitted after the first pilot study.
- January to December 2020: Complete follow-up interviews.
- Spring 2020 – Spring 2021. Write up papers.
- Autumn 2021: Write summary of PhD thesis research. Submit PhD thesis.
- The post-doc will be positioned with a two-year delay to await the on-going data collection.

Budget
See online application.

4. Key perspectives and compliance with strategic documents

Compliance with strategic documents
The project is in agreement with the Norwegian government's pronounced aim of making treatment of substance use and mental health disorders priority areas. This is intended achieved partly by strengthening the diversity in and to improve the quality of the treatment offered, including developing new, knowledge-based intervention methods [43]. Government documents also emphasize the importance of user involvement both on an individual level and to guide research in the field.

Relevance and benefit to society
Recognizing substance use disorder as a chronic, relapsing mental disorder, the effective treatment approaches should address both its biological, physiological and psychological domain components. This complexity calls for an integrative approach, and over the past thirty years NF training has surfaced as a medication free adjunct therapy to conventional intervention modalities for this patient group.

Preliminary clinical experience indicates that the method represents an intriguing, technology-intensive option and a refreshing alternative for a treatment-fatigued patient population, resulting from offering traditional "talk therapies" only. The proposed study will provide new knowledge about the use of neurofeedback in the treatment of SUD, specifically the novel infra-low training methods, potentially leading to a more holistic treatment approach, improved retention and relapse rates, and reduced detrimental outcomes for a vulnerable and difficult to treat group of patients.

Environmental impact
The study is not expected to constitute any additional hazard to the environment.

Ethical perspectives
Participants will be included after they have provided written informed consent to join the study. Approval has been sought from the Regional Ethics Committee. Based on six years of clinical experience and the outcome of the 2012 pilot study, no adverse side effects are expected for the patients. In order to secure equal treatment to all participants, the TAU group will be offered NF after

study completion. The project group has decided against including a placebo control in the study, as the practice of offering 20 sessions of non-active feedback was deemed unethical.

Gender issues
Participants of both genders will be included, and it is expected that the sample will mirror the typical gender distribution of patients referred to addiction treatment. A female clinician with a master's degree will be engaged as clinical coordinator for the study and will be the natural candidate for the doctoral research fellowship position.

Dissemination and communication of results
At least six scientific papers are planned to be written, three of which will form the basis for a PhD dissertation, and three for the post-doc position. All are intended to be published in international peer-reviewed journals, such as *Substance Abuse Treatment, Prevention, and Policy*; *Addiction Science & Clinical Practice*; *Journal of Psychiatry and Neuroscience*, and *Applied Psychophysiology and Biofeedback*. The results will also be communicated in relevant national and international research arenas and targeted to decision makers in the addiction and health fields, as well as to the existing clinical network and their associated websites and social media sites. Moreover, the results will be used to expand and improve the practice of neurofeedback for the addiction population by providing further documentation of its effectiveness.

Tentative titles for the papers are as follows:

1. "Feasibility and effectiveness of neurofeedback in substance use treatment: Experiences from a naturalistic pilot study"
2. "Clinical effectiveness of neurofeedback in a mixed substance abuse population as measured by quality of life. A randomized controlled trial"
3. "Do effects last? Follow-up results 12 months after completing a neurofeedback intervention program for substance use disorders"
4. "Can neurofeedback reduce psychological distress in patients with substance use disorders? Secondary outcomes of an RCT."
5. "Does cognitive function predict effectiveness of and treatment retention in a neurofeedback treatment regime?"
6. Hangin' in there: Can neurofeedback reduce drop-out rates and prevent relapse in addiction treatment? Assessment of costs and benefits.

Communication with users
Cooperation has been established with a user representative who has partaken actively in the entire research process. From an early phase, the representative has been instrumental in bringing in the user perspective in preliminary considerations, commenting on relevant questionnaires, thereby securing more useful outcome measures for the project. During the data collection phase, she will aid in the recruitment process and constitute a link to the research participants by taking part in patient interviews and screenings, encouraging their participation in the project, and highlighting its significance for the user population, both directly and through user organizations. Specifically, she is intended to play an active role in pre-treatment information and dialogue sessions, to which the NF-TAU participants are invited to discuss the program and ask any questions they may have concerning the intervention. She is also intended to aid in distribution of the results in relevant user forums in order to raise awareness of the method and its application for the SUD population. External user organizations will also play a part toward this end.

5. Additional information specifically requested in the call for proposals

A patient with a SUD is typically a frequent user of local health care services across his or her lifespan, and in comparison, the time spent in specialist treatment facilities is relatively short. A close cooperation between the services, both on a clinical level and with a view to research, is therefore paramount to treatment success with this patient group, and to secure life-long healing and QoL for the individual. In line with the Government's Coordination reform intentions, the neurofeedback intervention can be viewed as a potential addition to the support yielded at the municipal level,

reducing the need for these services and further strengthening the cooperation between the service providers[44]. Experience from the pilot study indicates that neurofeedback is welcomed by our local cooperating partners as a method for enhancing the function of their clients, and may thus serve as an additional useful tool in the continuum of care of the individual.

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