Study Protocol

Digital cognitive behavior therapy for prenatal insomnia symptoms:
A trial protocol

Clinicaltrials.gov #NCT02805998

This protocol follows the standardized SPIRIT 2013 guidelines for clinical trial protocols[1] and was developed based on the protocol submitted for IRB approval (7/8/16) and on the scope of work submitted for funding (4/25/16).

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The study funders had no role in the study design, collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Introduction

Background and rationale

Insomnia symptoms are prevalent during pregnancy, with as many as one in seven pregnant women reporting moderate-to-severe insomnia symptoms.[2] Insomnia is associated with increased risk of adverse maternal outcomes, including depression and preterm birth.[3,4] Pharmacotherapy is the most commonly used treatment approach for insomnia, but may be associated with adverse birth outcomes,[5] and perinatal women report a preference for non-pharmacological approaches.[6] Despite the well-documented link between poor sleep and adverse maternal outcomes, there is a paucity of randomized controlled trials investigating the impact of nonpharmacological insomnia treatment on antenatal insomnia.

A robust literature documents the efficacy of cognitive behavioral therapy for insomnia (CBT-I) compared to control conditions.[7] Additionally, mounting evidence has shown that CBT-I is associated with improved depression outcomes, including higher rates of depression remission among participants with insomnia and depression,[8] and lower depression symptom severity among non-pregnant adults with both insomnia and subclinical depression symptoms compared to digital attention-matched placebo control.[9] In a single group study, participants reported significant improvements in subjective and objective sleep parameters and depression symptom severity after five weekly sessions.[10] These results are promising, but the trial lacked a control group and therefore does not support causal inference.

Qualitative research shows that women report a preference for mental health care that includes flexible options.[11] Thus, digital programs may be of particular interest during the perinatal period. A recent meta-analysis supports the efficacy of digital CBT-I for sleep compared to control.[12] Sleepio is a digital CBT-I program associated with significantly greater improvements in sleep efficiency (among other sleep parameters) and depression symptom severity compared to both active control and treatment as usual conditions immediately post-intervention and at an 8-week follow-up.[13,14] The overarching goal of this project is to use a randomized control design to examine the efficacy of digital CBT-I (Sleepio) for sleep and mental health outcomes compared to treatment as usual among pregnant women with insomnia symptoms.

Objectives

Aim 1: To test the hypothesis that participants randomized to digital CBT-I will demonstrate significantly greater improvements in subjective sleep outcomes, including insomnia symptom severity (primary outcome), sleep duration, sleep efficiency, global sleep quality, and insomnia caseness, compared to TAU participants.

Aim 2: To test the hypothesis that participants randomized to digital CBT-I will experience significantly greater improvements in mental health outcomes, including depressive symptoms (primary) and anxiety symptoms, compared to TAU participants.

Aim 3: To explore the impact of digital CBT-I on birth outcomes. In response to research indicating that insomnia and poor sleep quality are associated with increased risk for preterm birth, we will compare rates of preterm birth, as well as other birth outcomes such as low birthweight, delivery method, and APGAR scores, between digital CBT-I and TAU participants. Because the sample size of the proposed study will be too small to draw conclusions, this aim is exploratory.

Trial Design

The study is a parallel group, superiority, randomized controlled trial of digital CBT-I versus TAU among pregnant women, with a 1:1 allocation ratio.

Methods

Participants, interventions, and outcomes

Study setting. All study activities will occur remotely via phone, website, and digital app.

Eligibility criteria. Inclusion criteria are: 1) self-reported pregnancy up to 28 weeks gestation, 2) 18 years of age or older, 3) meets DSM-5 criteria for insomnia disorder as determined by the Sleep Condition Indicator (women experiencing symptoms ≥ 1 month are eligible in contrast to DSM-5 criteria requiring symptom duration ≥3 months) **or** experiencing elevated insomnia symptom severity as determined by a total score ≥ 11 on the Insomnia Severity Index, and 4) has regular access to a web-enabled computer, tablet, or smart phone. Exclusion criteria are: 1) probable major depression as determined by a total score ≥ 15 on the Edinburgh Postnatal Depression Scale (EPDS), 2) self-reported bipolar disorder, 3) self-reported history of psychosis, 4) active suicidality defined as scoring > 1 on EPDS item 10, or report of a specific suicide plan or recent attempt, and 5) shift work employee.

Interventions. *Digital CBT-I.* The digital CBT-I program, Sleepio (www.sleepio.com), is delivered in 6 weekly web-sessions via website or iOS app. Treatment content is based on CBT-I manuals and includes a behavioral component (sleep restriction, stimulus control, and relaxation), a cognitive component (paradoxical intention, cognitive restructuring, mindfulness, positive imagery, putting the day to rest) and an educational component (psycho-education, sleep hygiene). The program is interactive, and content is presented by an animated virtual therapist. Participants schedule their session times and are prompted via email/SMS if they do not complete the session as scheduled. Participants complete daily sleep diaries throughout the intervention, which is used by the program to provide personalized help. Participants receive an email/SMS reminder each morning to prompt them to fill in their sleep diary. Additionally, study staff will monitor participant use of the website, and will contact any participants who have not logged on to the program or who have fallen behind in weekly sessions in order to discuss any challenges and troubleshoot barriers. Participants complete a short questionnaire at the beginning of the intervention to set treatment goals. Throughout the course of therapy, participants have access to an online community board and an online library of information about sleep. Participants will receive access to Sleepio at no cost as part of their participation.

Treatment as usual (TAU). The control condition is intended to reflect standard care for pregnant women with insomnia symptoms. No limits are placed on receiving non-study treatment, including medication or psychotherapy. Participants randomized to TAU will receive a free voucher code to Sleepio upon study completion.

Outcomes. The primary outcome is change in insomnia symptom severity (Insomnia Severity Index) from baseline to 10-weeks post-randomization. Secondary sleep outcomes include sleep efficiency (sleep diary), sleep duration (sleep diary), global sleep quality (Pittsburgh Sleep Quality Index), and insomnia caseness (Sleep Condition Indicator). Secondary mental health outcomes include depressive symptom severity (Edinburgh Postnatal Depression Scale) and anxiety (Generalized Anxiety Disorder Scale). We will additionally examine change to 18-weeks post-randomization, 36 weeks gestation, 3 months postpartum, and 6 months postpartum. Other, exploratory outcomes include birth outcomes, such as gestational age at delivery, APGAR scores, birthweight, and delivery method.

Participant timeline (See Figure). *Eligibility survey*. Individuals interested in participating will complete an electronic consent form describing the screening procedures. Next, participants will complete questionnaires to assess eligibility. Participants will complete a demographic measure, provide contact information, and indicate whether they agreed to be contacted for other research studies. Individuals who pass the eligibility survey will complete the study consent form and be given instructions to complete the sleep diaries.

Sleep diaries. Participants will receive email requests to complete sleep diaries on REDCap for seven consecutive days. Participants will indicate when they got in bed, how long it took to fall asleep, number of awakenings, duration of awakenings, final awakening time, and when they got out of bed. Participants who complete at least four diaries will be eligible to proceed to the orientation session.

Orientation. The primary goal of the phone orientation session, modeled after Goldberg and Kiernan (2005),[15] is to promote participant retention by discussing the importance of the trial, required commitments, what to expect if randomized to digital CBT-I or TAU, the rationale of the control condition and random assignment, and the impact of attrition bias. Participants will describe personal pros and cons for participating in the trial, and will be given as much time as needed to decide whether to participate.

*Baseline measures***.** Participants will complete baseline measures on the Qualtrics online survey system.

Randomization. Upon the participant's completion of the baseline measures, study staff will request the condition assignment from the independent investigator who generated the randomization sequence. Study staff will inform participants of their condition assignment by phone call and email.

*Follow-up assessments***.** Participants will complete all study measures and the daily sleep diaries at 10-weeks post-randomization, and all study measures at 18-weeks post-randomization, 36 weeks gestation, 3 months postpartum, and 6 months postpartum.

Sample size. Existing literature comparing CBT-I to treatment as usual suggests a large effect size (Cohen's *d*=0.95) for baseline to post-intervention differences and a medium effect size (Cohen's *d*=0.69) for baseline to 8-week follow-up on sleep efficiency.[13] As for depression symptom severity, existing literature comparing CBT-I to treatment as usual suggests a small to medium effect size (Cohen's *d*=0.20-0.69) for baseline to post-intervention differences and a medium effect size (Cohen's *d*=0.48-0.78) for baseline to 8-week follow-up.[9,14] Using G*Power for an ANOVA repeated measures with a within-between interaction, we estimated that 128 women were required to have 80% power to detect a small-to-medium effect size (Cohen's *d* =.30) with α=.01 for a within-between interaction. Attrition in web-based CBT-I programs ranges from 4-22%.[13,16,17] but a meta-analysis of computer-based treatments for depression estimated drop-out rates of 38.4% in programs that offer administrative support.[18] We used the higher attrition estimate of 38%, yielding a required sample size of 208 participants (n=104 per group).

Recruitment. We will utilize several recruitment methods to meet our target sample size. Although recruitment will focus mainly on the Bay Area, participants can enroll from anywhere because all study activities are completed remotely.

UCSF Outpatient Recruitment Program. Study recruiters will review medical records of women receiving prenatal care at UCSF. Women who may be eligible based off chart review (e.g., less than 28 weeks pregnant) will be approached in the clinic waiting area at the time of their appointment to be introduced to the study. Recruiters will give the patient an opt-in card

and a brief overview of the study. Patients who are interested in participating will be given information to complete the web-based prescreening online and/or will provide their contact information on the opt-in card to be contacted by study staff for more information.

Social media recruitment. We will identify blogs, websites, and social media accounts that serve the population we are targeting for recruitment (e.g., pregnant women) to host IRB-approved blog posts. Women interested in learning more will be directed to contact REST study staff directly or to complete the REST eligibility survey. Additionally, we will post IRB-approved text, blogs, and graphics on REST Study social media accounts (e.g., Twitter, Facebook, Instagram, etc.). We will also post IRB-approved links to educational articles about pregnancy, maternal mental health, and well-being with accompanying questions, which are designed to draw in and engage the population we are targeting for recruitment. In responding to any comments/questions, we will adhere to the same ethical principles as when responding to questions in standard, in-person recruitment efforts, and will encourage interested individuals to contact us directly by phone or email for more information. As described by Gelinas and colleagues (2017) we will uphold respect for the privacy and other interests of social media users and maintain investigator transparency.[19] We may also "like," "share," and "retweet" public posts by other users that are pertinent to insomnia or maternal mental health; when doing so, the posts will indicate that they are liked, shared, or retweeted from other users, and that the posts did not originate from REST Study Staff.

Participants will be recruited using paid and free advertisements including but not limited to: Craigslist, Facebook, websites of interest to pregnant women, listservs, Reddit, and Instagram. Advertisements will include IRB-approved recruitment text with a brief description of the study, study contact information, and a link to the web-based eligibility survey. Users may, with or without our awareness, share our study information.

Conventional, passive recruitment. Participants will be recruited via flyers, brochures, and postcards posted in community, medical, and retail settings serving a high volume of people (e.g., coffee shops, grocery stores, etc.), women who are pregnant (e.g., WIC, Black Infant Health, maternity clothing stores, etc.), and families (e.g., toy stores).

*Referrals from colleagues***.** We will also contact health care providers to ask if they would be willing to share our study information with any patients who may be interested.

*ResearchMatch***.** We will recruit participants through ResearchMatch, a national health volunteer registry that was created by several academic institutions and supported by the U.S. National Institutes of Health as part of the Clinical Translational Science Award (CTSA) program. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible. We will use IRB-approved text in these ads.

Clinical & Translational Science Institute (CTSI) Consultation Service, Direct Mail. We are collaborating with the CTSI Consultation Service to provide cohort identification and direct mail for recruitment. A Dear Patient letter will be sent to individuals identified from the APeX record systems via a data extraction by the Academic Research Systems (ARS) of patients who are pregnant. These patients are not known to or under the care of the researcher team. The CTSI Consultation Service will coordinate the mailing on behalf of the study. Interested subjects will contact study staff as described in the letter. The data extract will be delivered to the CTSI Consultation Service's MyResearch account in order to facilitate the direct mail activities while ensuring privacy and confidentiality of the patients identified.

Other direct mail and email services. We will collaborate with other businesses and organizations that provide direct mail and/or direct email services to our target population, including but not limited to: Lorton Data and Bay Area Parent Magazine.

*Informational talks***.** Study staff may provide information about the study at groups attended by pregnant women (e.g., at Babies R Us). Information provided will be consistent to what is described in recruitment flyers, consent forms, and orientation call.

Electronic health record recruitment. MyChart (APeX) will conduct a search for patients based on the study's inclusion and exclusion criteria. This is a completely computer-aided search, meaning the computer— not a person— searches patient charts. When a patient is identified as potentially eligible, they will receive an email from MyChart that asks them to log in to MyChart to read about a study in which they might be interested. The email is short and is the same for every recipient—it contains no patient-specific or study-specific information. When the patient logs into MyChart, there will be a "Research" tab with template information about research participation and how to opt out of receiving recruitment messages. The patient can click through to learn about the specific study to which they have been matched. The patient has the option of clicking a button to let the study team know that they are interested in learning more about the study. The study team will only receive information about the patient if the patient takes this action. If the patient clicks "No thanks" or simply does not respond, they will not be contacted by the study team or receive any follow-up emails from MyChart about the study, nor will their information be shared with the study team.

Assignment of interventions

Allocation. The blocked randomization sequence will be generated by an independent investigator using Sealed Envelope.[20] The randomization sequence and block sizes will be concealed from study staff. The randomization sequence will be kept on an electronic file inaccessible to the study staff. Once a participant completes baseline measures, study staff will request the allocation assignment from the independent investigator. Study investigators and staff will not be able to influence randomization or have access to future allocations.

Blinding. For study administration purposes, staff will be unblinded to participant condition assignment after allocation. Study staff will be blinded to outcomes during the trial. Participants will be unblinded to condition assignment due to the nature of the comparison group, which is not an active comparator. The study statistician will remain blinded to condition assignment for all primary analyses.

Data collection, management, and analysis

Data collection methods. Participants will complete study measures using the Qualtrics amd REDcap survey systems, which allow participants to read questions on the screen and press the response buttons to answer. Response validation will be utilized so that participants can only enter values within range for each item. To reduce missing data, responses will be requested for each item.

Subjective sleep outcomes. The primary efficacy outcome is insomnia symptom severity, as measured by the total score on the Insomnia Severity Index (ISI).[21,22] The ISI is a seven item measure that assesses symptom severity, satisfaction with sleep, impairment caused by symptoms, distress caused by symptoms, and the extent to which others have noticed symptoms over the last two weeks. A total score is computed by summing all items. Scores ≤ 7 indicate no

clinically significant insomnia, 8-14 indicate subthreshold insomnia, 15-21 indicate moderate severity insomnia, and ≥ 22 indicate severe insomnia.

Secondary sleep outcomes are sleep efficiency, nightly sleep duration, global sleep quality, and insomnia diagnosis. Daily sleep diaries will be used to measure sleep efficiency and sleep duration. Sleep efficiency is calculated by dividing the amount of time sleeping in bed by the total amount of time spent in bed and multiplying by 100. Scores range from 0-100%, with 85% and above considered normal. Sleep duration is the total amount of nightly sleep in hours. Global sleep quality will be measured using the Pittsburgh Sleep Quality Index (PSQI), a 19-item measure comprised of seven components assessing sleep duration, disturbance, latency, efficiency, quality, days of dysfunction due to sleepiness, and needing medication to sleep.[23] Each component score ranges from 0-3, and the components are summed to create a PSQI global sleep quality score ranging from 0-21. Higher scores indicate worse global sleep quality, and scores above 5 indicate poor sleep. To measure possible cases of DSM-5 insomnia disorder, we will use the Sleep Condition Indicator (SCI). [24] By adding a ninth item to assess early-morning awakening, the Sleep Condition Indicator can be used to identify possible cases of DSM-5 insomnia disorder.[24]

*Mental health outcomes***.** Depressive symptom severity will be assessed using the Edinburgh Postnatal Depression Scale (EPDS).[25] The EPDS is a 10-item self-report measure that omits depressive symptoms that can be conflated with normal pregnancy symptoms (e.g., appetite disturbance). It is frequently used to assess depressive symptom severity during pregnancy. Total scores range from 0-30, with higher scores indicating higher symptom severity. Scores of 10 or greater suggest minor depression, and scores of 15 or greater suggest major depression among pregnant women.[26] Anxiety symptom severity will be assessed using the Generalized Anxiety Disorder Scale (GAD-7).[27] Scores range from 0-21 with higher scores indicating higher anxiety symptom severity. Scores of 0-4 suggest minimal anxiety, 5-9 suggest mild anxiety, 10-14 suggest moderate anxiety, and 11-21 suggest severe anxiety.

All study measures will e self-report and collected via online survey systems. With the exception of the sleep diaries, which will be collected via REDCap, study measures will be administered via Qualtrics.

*Use of non-study treatments***.** At each follow-up assessment, participants will be asked about their use of the following aids to improve sleep: sleep medication prescribed by a doctor; combination sleep aid and pain reliever; over-the-counter or store-bought sleep aid; alternative therapy or herbal supplement; therapy or counseling; alcohol, beer, or wine; eyemask or ear plugs; other. Participants were also asked about their use of the following aids to improve mood: antidepressant medication, therapy or counseling; support group; alternative therapy or herbal supplements; other. Response options are 'rarely or never,' 'a few nights a month,' 'a few nights a week,' and 'every night/almost every night.'

*Obstetric outcomes***.** Obstetric outcomes will be assessed via medical record review, and include but are not limited to the following outcomes: gestational age at delivery, APGAR scores, birthweight, and delivery method. Participants will also self-report birth outcomes in case we are not able to obtain their medical record data.[28,29]

Participants will be sent reminders via their preferred method of communication after 3, 5, and 10 days of non-response. After 2 weeks of non-response, we will contact their secondary contact person. After 3 weeks of non-response, we will mail the primary outcome measure with a stamped and addressed return envelope. Every effort will be made to obtain outcome data from

participants who discontinue the intervention. If need be, participants who discontinue the intervention can opt to only complete the primary outcome measure to reduce time burden.

Data management. Qualtrics maintains data behind a firewall. All data is accessed only by the owner of the survey who must provide a user ID and a password. All pieces of data are keyed to that owner identification and cannot be accessed by anyone else.

REDcap is housed in a locked and guarded data center staffed at all hours. Entrance to the data center requires use of a card key to unlock the data center door and a second card key lock secures the cage that the servers reside within. The security of the data center is further protected by an Operations desk that is staffed 24x7 and by a security camera system. REDcap servers are guarded by multiple firewall and intrusion detection systems. All electronic connections to the REDcap environment are encrypted. The REDcap production system is comprised of a web server front-end and a MySQL database server back-end. The web server resides in a demilitarized zone to ensure that survey participants are able to access REDcap surveys from any device connected to the Internet. The MySQL server back-end resides in the protected ISU subnet that is protected by UCSF maintained firewalls. The data stored in the REDcap MySQL database server can be accessed by the REDcap end users by logging in and opening the REDcap project(s) that they have been granted access to by the owners of the projects. Only ITS and ISU system administrators are authorized to access the back-end database server directly by logging into the virtual private network for the database server resides in.

Statistical methods. Independent samples t-tests and chi-square tests will be used to examine between-group differences in baseline sociodemographic and clinical characteristics. Linear mixed effects models will be used to examine whether within-woman changes in sleep and mental health outcomes differ between the digital CBT-I and treatment as usual groups.[30] Models will include the sleep and mental health outcomes as the dependent variables, along with time, intervention group, and time by group interactions as the predictors. The models also will include random intercepts to accommodate the correlation among the repeated responses within women. The regression coefficients of time by intervention group interactions measure the differences in the rate of within-woman change in the outcomes between the two intervention groups. We will assess the statistical significance of the time by intervention group interaction using likelihood ratio tests. The primary analysis will assess differences in changes in insomnia symptom severity from baseline to post-intervention with time measured in weeks. Secondary analyses of additional sleep and mental health outcomes will use the same time scale. Additionally, we will examine change from baseline to follow-up.

Monitoring

Harms. Adverse events that are spontaneously reported by participants will be characterized by an independent safety officer as unexpected or expected, and causes will be characterized as definitely related, probably related, possibly related, or unrelated to study participation. Adverse events that are determined to be unrelated to study participation are documented but not reported to the IRB. All other adverse events are reported to the IRB.

Ethics and Dissemination

Research ethics approval

The research protocol will be submitted to the UCSF institutional review board for approval.

Protocol amendments

Protocol modifications will be communicated to all study investigators and approved by the IRB prior to implementation, and the trial registry will be updated accordingly.

Consent or assent

Individuals interested in this study will view an electronic consent form that describes the screening procedures. Participants who pass the web screening will next view a consent form describing all remaining study procedures. In both consent forms, participants will be encouraged to contact the PI with any questions. At the end of the forms, participants will be given options to indicate whether they decline or agree to participate in the study. Participants will have the option of downloading a copy of the electronic consent forms.

Participants recruited through UCSF outpatient OB/GYN clinics will additionally be asked to sign a HIPAA authorization form to enable us to request prenatal care and labor and delivery records. Participants will be mailed this form to read and sign and then mail back to us using a stamped and addressed envelope that we provide. Participants will be encouraged to contact study staff with any questions.

Confidentiality

Information provided on the Sleepio website is stored in encrypted form on secure servers located in the US. All passwords are stored in encrypted form and all sensitive traffic is transmitted securely via SSL by default. Data may be transferred to, and stored at, other destinations or to staff who work for Big Health or one of their suppliers. Such staff may be engaged in, among other things, the provision of support services. By submitting personal data, participants agree to this transfer, storing or processing. Sleepio will use strict procedures to prevent unauthorized access in accordance with their Company data protection policy and code of practice, and responsibilities as a registered Data Controller in the UK. Despite these measures, the transmission of information via the internet is never completely secure.

Hardcopy data will be stored in a locked file cabinet and/or in a locked office and in a locked suite, and will include the participant's study identification number. All data will be entered into or collected in electronic form. Electronic data will be stored on a private, password-protected hard drive accessible only to the PI or trained researchers in the lab. Only de-identified data will be used in publications. De-identified data will be shared between collaborators in order to facilitate collaboration with respect to data management, cleaning, analysis, and manuscript preparation. The subject's name, contact information, and ID will be recorded indefinitely on an electronic linkage file stored on an encrypted hard drive or secure online server.

Declaration of interests

The investigators report no competing interests.

Access to data

The principal investigator will retain access to the final trial data set, and there are no contractual agreements limiting such access.

Ancillary and post-trial care

No provisions are made for ancillary or post-trial care or for compensation to those will suffer harm from trial participation.

Dissemination policy

Trial results will be submitted to peer-reviewed journals for publication. Investigators will collaborate with the UCSF and Preterm Birth Initiative media resource offices to develop press releases for resulting publications. Trial results will also be shared with trial participants via email.

We will utilize the International Committee of Medical Journal Editors guidelines for determining authorship eligibility and we do not intend to use professional writers.

Individuals interested in obtaining the de-identified participant-level data set and statistical code will be instructed to contact the Principal Investigator.

Protocol Amendments

The following amendments were made to the protocol after participant recruitment began:

1. March 10, 2017: First, in order to enroll women whose insomnia symptoms onset during pregnancy, we changed the inclusion criteria to state that women who indicate on the SCI that they have experienced insomnia symptoms ≥ 1 month will be eligible, in contrast to DSM5 criteria that requires insomnia symptoms ≥ 3 months. Second, to reduce attrition, we added that we will collect extensive locator information from participants at baseline. Specifically, we will collect the phone number and email address of one social/family support member, and request permission to contact this person if we lose touch with the participant. Participants can decline to give this information and still participate. This is a common practice in clinical research trials, and especially important in digital interventions that are prone to high attrition.
2. June 20, 2017: We modified our eligibility criteria such that participants must **either** meet criteria DSM-5 criteria for insomnia as determined by the Sleep Condition Index **or** score ≥ 11 on the Insomnia Severity Index (ISI).
3. February 8, 2018: To maximize completion of study outcome measures and avoid attrition bias, we modified study procedures to allow us to mail a paper copy of outcome measures with a stamped and addressed return envelope.
4. March 27, 2018: As we neared our enrollment target (randomizing 183 of 208 women), we modified our eligibility criteria to focus our remaining enrollment on Black women, who were under-enrolled to date. Existing recruitment strategies identified Black women but at a slower rate compared to White women.

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