SDRAB Meeting Workshop Report:
Sleep in a Bottle?: Research needs and gaps in ingested, non-prescription strategies for healthy sleep
Workshop dates: September 15, 16, 2025

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National Institutes of Health
Office of Dietary Supplements

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Quantity of Melatonin and CBD in Melatonin Gummies Sold in the US

Pieter A. Cohen, MD[1]; Bharathi Avula, PhD[2]; Yan-Hong Wang, PhD[2];
Kumar Katragunta, PhD[2]; Ikhlas Khan, PhD[2]

"Prior to the COVID-19 pandemic, melatonin was used by an estimated 1.3% of children in the US, most commonly for sleep, stress, and relaxation.[1,2] Despite the lack of high-quality evidence to support melatonin's efficacy for these indications in healthy children, use increased during the COVID-19 pandemic.

Calls for pediatric melatonin ingestions to US Poison Control Centers increased 530% from 2012 to 2021 and were associated with 27,795 emergency department and clinic visits, 4,097 hospitalizations, 287 intensive care unit admissions, and 2 deaths.[3]"

Why focus on ingestibles when CBTi works?

- 1 in 5 US adults use either prescription or OTC sleep aids

- In the 2002 NHIS 64.8% of people who reported insomnia or trouble sleeping used "biologically-based approaches" (mostly ingested products such as herbs, nutritional products)

- Nutrition Business Journal reports strong sales of DS for "Sleep Health" (> for brain health or healthy aging, < for weight loss)

- Over 2% (nearly 2700) products in ODS' DSLD are labeled for sleep use

- What are these products? Are they safe? Effective?

DS in DSLD with "sleep" on the label

Total number of on-market sleep advertised products: **2,685**

- Melatonin: 1,402 (52%)
- Magnesium: 577 (21%)
- GABA: 360 (13%)
- Botanical ingredients:
  - # of ingredients that appear in ≥ 100 products: 8
  - # of ingredients that appear in 50-99 products: 10
  - # of ingredients that appear in 10-49 products: 50
  - # of ingredients that appear in 5-9 products: 39
  - # of ingredients that appear in 2-4 products: 98
  - # of ingredients that appear in 1 product: 74

4 products	3 products	2 products		1 product		
Buckthorn	Anise	Agaricus	Indian tinospora	Achillea millefolium	Lemon myrtle	Geranium root
Camphene	Apocynum venetum	Amber resin	Isatis	Acorus calamus	Logan	Spikenard
Capsicum annuum	Arrhenatherum	Amla berry	Long pepper	Albizia julibrissin	Longan	Suan zao ren
Chokeberry	Black elder	Aronia	Montmorency cherry	durazz	Luo han guo	Szechuan lovage root
Corydalis	Blessed thistle	Aster alpigenus	Mugwort	Barley malt	Maca	Tilia tomentosa
Cynanchum wilfordii	Cascara sagrada	Atractylodes	Nelumbo nucifera	Biota	Madagascar vanilla	Tremella fuciformis
Eucalyptus	Ceramosides	Barberry	Nettle	Bitter blocker	extract	Tripterygium wilfordii
Garcinia cambogia	Chaga	Basil	Nutmeg	Black nightshade	Maritime pine bark	Vidanga
Garlic	Citronellol	Bayberry	Phragmites	Blue lotus	Millet	Woad
Guggul	Cutch tree bark	Black root	Pumpkin seed	Bupleurum	Mistletoe	Wuhan tonify wei qi
Horsetail	Devil's claw	Bladderwrack	Sage	Caraway	Muira puama	tang
Indian gooseberry	Epimedium	Blue malva flower	Salvia sclarea	Chebulic myrobalan	Mulungu bark	Yacon syrup
Ligusticum wallichii	koreanum	Ceratonia siliqua	Siberian rhodiola	Christmas rose	Mung bean	
Longjack	Eucommia ulmoides	pod	Slippery elm	Cissus	Mustard seed	
Motherwort	tree	Chicory	Thyme	quadrangularis	Nigella sativa	
Noni	Grassleaf sweetflag	Cnidium monnieri	Wheat grass	Citicoline	Olea europaea	
Oat milky seed	Gymnema	Codonopsis		Costus	Ophiopogon	
Phlomis umbrosa	Honeysuckle	Coptis		Cumin	Paeonia lactiflora	
Sceletium tortuosum	Horse chestnut	Coriander		Dodder seed	Paprika	
White willow	Lemon verbena	Crocus sativus		Dwarf lilyturf	Partridgeberry	
	Lobelia	Dwarf morning glory		English hawthorn	Phytosterol	
	Marshmallow	Eclipta		Feverfew	Picrorhiza kurroa	
	Oriental arbor-vitae	Eurycoma longifolia		Fig tree	Red root	
	Pasque flower	Ficus benghalensis		Figworts	Rheum palmatum	
	Platycodon	Finger-leaf morning		Gentian	Rooibos	
	grandiflorus	glory		Goldenseal	Rose hip	
	Poppy	Forskolin		Grapevine	Safed musli	
	Pygeum	Forsythia		Gum resin	Sandalwood	
	Safflower	Guarana		Huperzia serrata	Sesame	
	Shilajit	Guggulipid		Hyssop	Sheep sorrel	
	Soursop	Hibiscus		Indian jalap	Sophora japonica l.	
	Stinging nettle	Horehound		Indian sarsaparilla	South african	
	Wild yam	Horny goat weed		Jamaica dogwood		
	Zea mays	Horseradish		Kratom		

Workshop Agenda: Day 1

- **Scope of the Problem: Prevalence, Causes, and Consequences of Poor Sleep Health**
  - Dan Buysse, Orfeu Buxton, Aric Prather

- **Ashwagandha to Zinc and Outside the Bottle: Strategies People Use to Improve Sleep**
  - Michael Grandner, Michael Heinrich, Todd Arnedt, Christopher Scott Colwell, Mary Paine

- **Melatonin mini-session**
  - Judith Owens, Jeanne Duffy

- **Lightning product proposals**
  - Chengguo Xing (kava kava), J. Kent Werner (magnesium)

- **Overview of Mediators, Mechanisms and Targets for Sleep Interventions**
  - Philip Cheng, William Wisden, Jason Gerstner, Dragana Rogulja

Link to Agenda

Workshop Agenda: Day 2

- **Epidemiological, Nutritional and Ethnobotanical: Exploring Application of 21st Century Methods and Traditional Uses to Query Gaps in Knowledge of Potential Sleep Remedies**
  - Ina Vandebroek, C. Benjamin Naman, Steve Tsang, Jeran Stratford, Angus Burns

- **Relevant Clinical Datasets**
  - NHANES, MHANES, Nutrition for Precision Health, ECHO, ABCD study

- **Preclinical Approaches: Exploring Application of New Approach Models to Gaps in Knowledge of Over-the-Counter Products Used for Sleep**
  - Yitong Liu, Alysson Muotri, Roger Linington, Doris Kretzschmar

- **Approaches to Accelerate Learning from Clinical Trials**
  - Chris Coffey, Miguel Hernán, Jeff Chen

Link to Agenda

Workshop Stats

Day 1

- 452 attendees
- 16 presenters

Day 2

- 327 attendees
- 18 presenters

Needs and gaps

Sleep in a Bottle?:

Research needs and gaps in ingested, non-prescription strategies for healthy sleep

Research needs - overall

- Objective measures of sleep sufficiency - replicable, validated, preferably scalable (portable, inexpensive)
- Include both objective/quantitative AND subjective/PROs in clinical trials
- Longitudinal studies and trials
- Inclusion of participants across the lifespan and other subpopulations (e.g., pregnancy)
- More study of wearables: validation, standardization, harmonization, raw data and processing algorithms should be FAIR
- Validated approaches to combine sleep and dietary intake data from large data sets to explore for associations

General, Major Gaps

- Epidemiological data – what OTC products are people using for sleep?
- Replicated data on safety, sleep effects of natural products – including effects of Cannabis products on sleep
- Generally little rigorous data on potential mechanisms of botanicals, including evidence re active compounds, targets, biological/behavioral effects, dose-response, ADME, PK, potential for drug and/or food interactions
- Product integrity – chemistry to control for efficacy, bioavailability, safety, monitoring for contaminants and adulterants – about 1/3 of lavender products adulterated in recent study (Jalil & Heinrich, Eur J Pharm Sci 2025)
- Higher throughput approaches to screen ingested products for likelihood of sleep activity – in silico, organoid, model organisms, esp. Drosophila

Gaps and needs: Alcohol

Gap: There is a lack of studies with objective sleep outcomes

Use for sleep has increased significantly in the past 20 years

Common, but used less often than Cannabis and other natural products or OTC medicines

Research needs:

- Longitudinal studies w/ objective (& PR) outcomes, effective placebo (or other) controls and checks on control credibility
- Studies of long-term effects

Gaps and needs: Cannabis

47% of US adults using medicinal Cannabis report having insomnia

Research gap:

Rigorous clinical trials with effectively blinded controls, chemically well-characterized product, objective as well as PR sleep outcomes

Research need:

As above, with dose, circadian timing and route of administration optimized

Gaps and needs:
Kratom (Mitragyna speciosa)

- Increased use in US from 3-5 million in 2016 to 11-15 million users in early 2023.
  - Commonly used for chronic pain, opiate addiction

- Interacts with α-adrenergic, dopaminergic, and serotoninergic receptors as well as opioid receptors
  - Stimulant at low doses; possible "opioid sparing agent" at higher doses

- No serious AEs but risk of drug interactions
  - Exploration of addiction-related effects

Research need: RCT of existing well-characterized products with dose-ranging, objective outcomes for sleep, PRO for sleep and pain

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Gaps and needs: Melatonin

Jeanne Duffy, Brigham and Women's Hospital and Judith Owens, Harvard Medical School

Most commonly used in US, often combined with other ingredients: 20% of children received melatonin from parents in last month in 2024 survey, half of these without healthcare provider recommendation

- Strong evidence for circadian shifts (e.g., jet lag, shift work)
- Negligible differences in adults taking 0.3 vs. 5.0 mg doses

Research gaps:

- Effects on sleep maintenance, wake after sleep onset, sleep duration, sleep efficiency: these are *not* well documented

- Effects of long-term use

- RCTs in children with insomnia, neurodevelopmental disorders, medical and psychiatric comorbidities with comparators

- Dose response data

- Treatment combination studies

Practitioner need: clear, evidence-based guidelines for pediatric providers
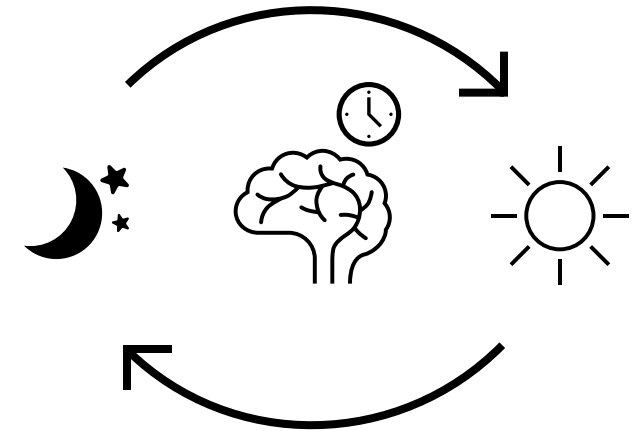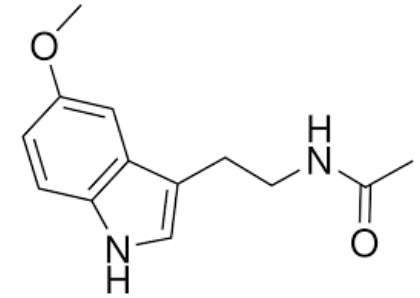
Higher throughput translational models with potential to screen interventions for potential efficacy, target engagement

Day 2, Session 2: Yitong Liu (FDA), Alysson Muotri (University of California), Roger Linington (Simon Fraser University)

Goals: Screening for relevant active compounds to support reproducibility, bioavailability, safety, PK/PD, drug interactions

NAM and in silico models

- Biological and toxicological pathways and mechanisms of action for isolated botanicals, but cannot currently model synergistic interactions

- NP Analyst to predict which compounds have which biological activities. The method is chemistry- and mechanism-agnostic and can be applied to any model.

- Cortical organoids: can include multiple neuronal cell types as well as glia, show oscillations in melatonin and cortisol

Approaches to Accelerate Learning from Clinical Trials

Day 2, Session 3: Chris Coffey (University of Iowa), Miguel Hernán (Harvard), Jeff Chen (Radicle Science)

- Clinical trials are large, expensive, and time-consuming

- Adaptive designs offer flexibility
  - Master protocol for multiple interventions or subtypes
  - Platform trials to evaluate multiple therapies and/or subpopulations

- Target trial emulation

- Decentralized trials
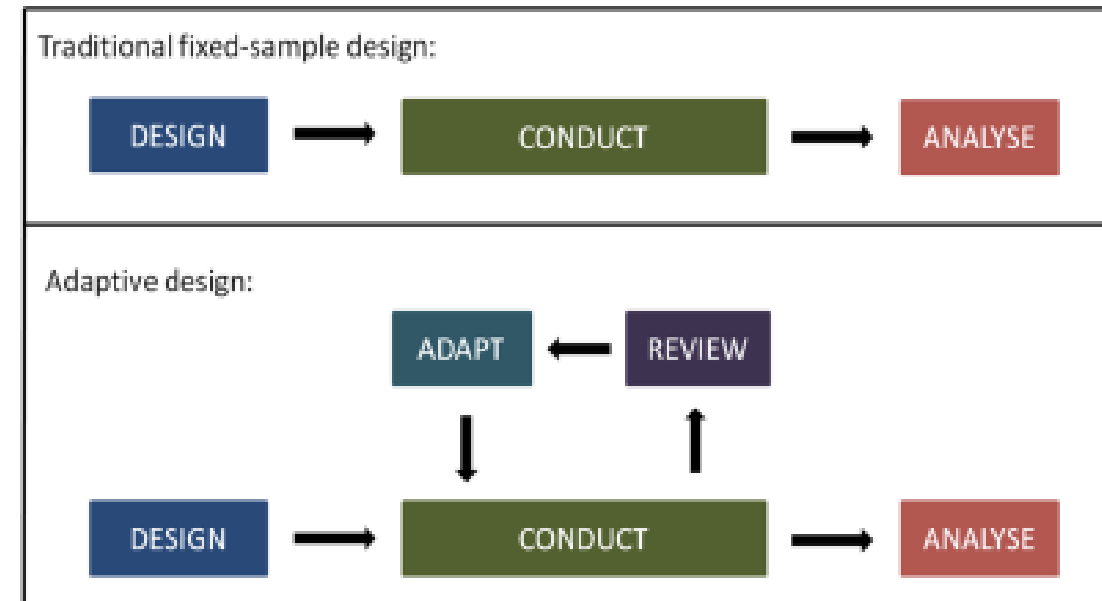
Pallmann et al (2018), *BMC Medicine*, 16(1):29.

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Thank you! Contact us:

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Non-mammalian models to study sleep

Doris Kretzschmar (Oregon Health & Science University)

Zebrafish

- Actigram and electrophysiological activity
- Sleep waves that resemble human REM- and NREM-like activity
- Same neurotransmitters as humans
- Problems: aquatic environment; gene duplication

Drosophila

- Video tracking
- Similar sleep fragmentation and total sleep time