Bacopa monnieri and Centella asiatica use as a Possible Nidus for Psychosis?

Joseph Kramkowski MD PGY2[1], Nadia Sion MD PGY1[1], and Samuel Lin MD[1]
[1]Pine Rest Christian Mental Health Services/Michigan State University

Background

- Plants have been an integral compound in the development of what we know as modern medicine, with written texts concerning medicinal plants dating back approximately 5000 years.[14] Ancient Ayurvedic, Chinese, Arabian, Egyptian, and Sumerian texts all have references to compounds whose indication is to improve cognition.[1] The modern "nootropic" market has grown to include plant and lab prepared compounds that are unregulated by the FDA. These supplements are available to the consumer regardless of age or education, as evidenced by a Google search for "nootropic store" netting over 2 million results.[12]

What is a nootropic?

- **Nootropic**, of Greek origin, has a basic translation of "to bend or shape the mind," also called cognitive enhancers or "smart drugs," are compounds both plant and lab derived that aim to improve one's neurocognitive abilities.[18] These are both; FDA approved, such as modafinil and methylphenidate, and not FDA approved, such as piractem, sesame, or ashwaganda.[15, 17]
- Commonly administered as a pill, but some as a tea, tinuture, cream, or ointment.[9,19]
- With these compounds both referenced as "brahmi" in Sanskrit Ayurvedic literature, there is discord whether "brahmi" is Bacopa monnieri, Centella asiatica, or a combination of the of two.

Bacopa Monnieri

- Plant: Water hyssop
- Mechanism of action: Bacosides,[2] the proposed active component of Bacopa monnieri is proposed to increase GABA and modify "acetylcholine release, choline acetylase activity, and muscarinic cholinergic receptor binding." Inhibition of acetylcholinesterase has been documented in in vitro studies.[8]
- Proposed neuropsychological indications: Greatest effectiveness is proposed in the language neurocognitive domain. Among the many domains that Bacopa monnieri has been proposed to effect learning and memory, attention, and executive functioning are three cognitive domain where Bacopa monnieri has literature to support its claims.[1,8] Multiple studies, including systematic reviews, randomized, double blind, placebo controlled, (non)crossover trials, phase 2 trials, open label trials and reviews have shown improvement in language domains, some even obtaining results similar to donepezil.[1] Multiple animal studies[5,6] and 1 case report[4] show possible antipsychotic properties.
- Dosing**(these are theoretical doses demonstrated in studies and not FDA approved)**:
  - Adult: Up to 600 mg daily for max 12 weeks.[8]
  - Children: Up to 225 mg for 6 months.[8]
- Neurological adverse reactions: drowsiness, headache, insomnia, and vivid dreams.[8]

Centella Asiatica

- Plant: Gotu Kola or Indian pennywort,[19] is a member of the parsley family.[9]
- Mechanism of action: Theorized to be protective from glutamate-induced oxidative damage and combat build of beta-amyloid. In vitro, activity has been seen at cholecystokinin and GABA receptors.[9]
- Proposed neuropsychological indications: Neuroprotection, depression, "nootropic activity," epilepsy, and as a sedative.[13] A randomized, placebo controlled, double blind study revealed improvements in mood and cognitive function, a double blind placebo controlled study reveal anxiolytic properties and a open label study showed improvement in mild cognitive impairment and "well being."[19]
- Dosing**(these are theoretical doses demonstrated in studies and not FDA approved)**:
  - Extract or tincture: up to 180 mg daily for 12 months or 1 g daily for 60 days.[9]
  - Dried plant: up to 2.2 g daily for 4 weeks.[9]
  - Also available in creams and ointments.[9]
- Adverse reactions: No neurological adverse reactions found, however night eating syndrome was seen in one case report. Proposed moderate interaction resulting in sedation from increased effect of central nervous system depressants.[9]

Case Report

Chief Complaint: "trying to figure out what my memories are"

HPI: 22-year-old Caucasian male presents for voluntary psychiatric hospitalization, at the prompting of his mother, with symptoms including poor sleep, paranoia, and religious preoccupation. Utilizing Bacopa monnieri 5 g daily for six months and an unknown amount of Centella asiatica daily. Reports taking these medications to feel "numb and calm," promote "neuroplasticity," and help "figure out what my memories are." Reports 3-4 hours of poor sleep nightly and poor appetite. Describes erotomanic delusions, paranoia, thought disorganization, religious preoccupation and passive suicidal ideation with no plan or intent. Endorses delusions of reference involving social media posts from old friends that he believes are speaking directly to him, becoming fixated on these individuals. Reports significant anxiety with ruminating, intrusive, and racing thoughts described as "obsessive." Self-reports a down and sad mood, though denies feelings of worthlessness or hopelessness. Negative for past manic symptoms or hallucinations.

Current Medications: Only taking nootropic supplements

Past Psychiatric History:

Diagnoses: Major Depressive Disorder, Generalized Anxiety Disorder and Attention Deficit Hyperactivity Disorder, and Dyslexia.

Medication trials: escitalopram, paroxetine, bupropion, alprazolam, lisdexamfetamine and amphetamine/dextroamphetamine mixed salts

Family Psychiatric History: Maternal and paternal anxiety

Social History: Has a bachelor's degree and currently in an internship. He is single with no children. Denies all substance use including illicit drugs, tobacco and alcohol.

Diagnostic Testing:

Vitals(at intake): Hypertensive(145/87), otherwise unremarkable.

Labs: UDS, COVID-19, TSH, CMP, and CBC were unremarkable.

Imaging: CT head was unremarkable.

Mental Status Exam: Patient was disheveled with slow rate of speech and flat affect. Reported erotomanic delusions, paranoia, delusions of reference. Thought process was illogical and disorganized and he was perseverative. Fair insight as he was aware of his symptoms but unable to discern whether his delusional thoughts were reality. Appeared internally preoccupied and repeated questions before responding. Fair memory as he recalled some but not all biographical information. Endorsed passive suicidal thoughts with no plan or intent.

Assessment: Working diagnoses included Unspecified Schizophrenia Spectrum and Other Psychotic Disorder and Substance/Medication-Induced Psychotic Disorder, rule out.

Hospital Course: Initially started on aripiprazole for 2 days, but with continued insomnia, high anxiety and racing thoughts. Subsequently transitioned from aripiprazole to quetiapine to better target mood, psychosis and insomnia. Initial dose was quetiapine 150 mg once nightly with 50 mg three times a day as needed for anxiety or sleep. Patient became fixated on the half-life of quetiapine and minimized the need for psychotropics, despite his high level of anxiety and continued delusions. Given the patient's reservations about medications, psychopharmacologic education was provided and patient became agreeable and understanding of the treatment plan. Quetiapine was slowly titrated to eventual dosing of 50 mg in the morning, 50 mg in the afternoon and 400 mg at night. Upon discharge, patient reported improved mood stability and sleep, and was denying paranoia, ideas of reference, or other delusions.

Discussion

Patients may not understand the ramifications of using widely available over the counter nootropics. While some of these compounds have been used for millennia,[1] many do not have established pharmacologic properties. Furthermore, the sellers of nootropics advertise the proposed effects of the compounds using verbiage such as "quality," "pure," and "guaranteed."[11] Many also provide dosing guidelines, while stating that the Food and Drug Administration has not assessed these compounds. Lastly, these sellers do not typically list adverse effects of their products.

When applying this to our patient, he was ingesting levels of Bacopa monnieri and Centella asiatica well beyond recommended doses.[8,9] With theoretical or controversial mechanisms of action for these compounds it is difficult to explain how they would influence psychotic symptoms. GABA has been seen to be in higher levels in actively manic patients[7], with each of these compounds being linked to elevated levels of GABA or binding to GABA receptors[8,9] was our patient experiencing a mixed manic episode? Or did the Centella asiatica's possible increase of dopamine[10] lead to psychotic symptoms? Without well vetted pharmacokinetics and FDA oversight, we are unable to point to any one etiology. Thus, we present this case to highlight a possible connection between Bacopa monnieri or Centella Asiatica and psychotic symptoms. We hope to add to the body of literature on the compounds while encouraging providers to inquire about usage in their own patients.

Clinical Pearls

- **Nootropics are widely available but not FDA-approved or regulated**
- **Patients may seek out nootropics as a less burdensome and less expensive route to treatment (Figure 1)**
- **Routine screening for nootropic and other supplement usage is important as part of a psychiatric assessment**
- **Nootropic use, especially beyond typical dosing ranges, may contribute to psychosis and other psychiatric symptoms**

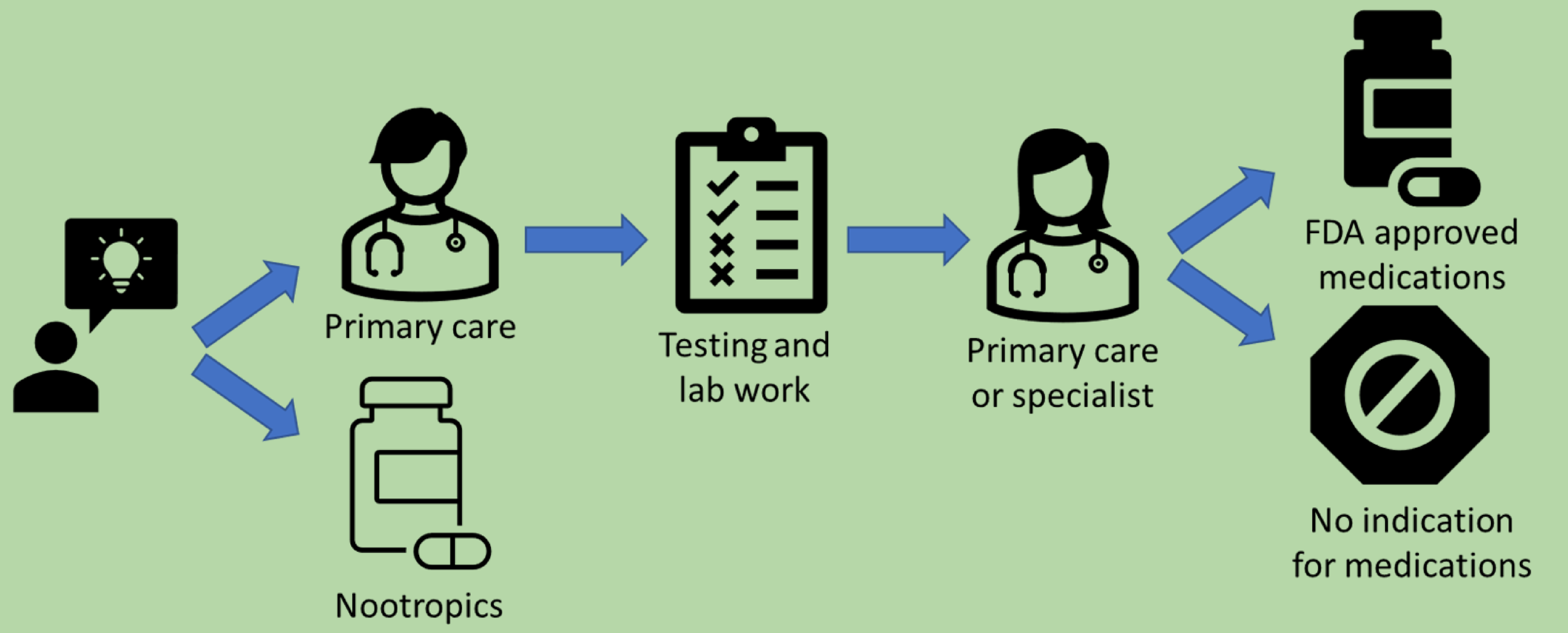

Figure 1. Patient dilemma of a lengthy and possible costly route to FDA approved medications or widely available inexpensive nootropics

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