

New Approaches to Depression and a Novel Antidepressant: Deuterium Oxide

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THE PROBLEM

- Mood disorders are one of the most disabling of the world's diseases
Each year over 1 in 12 adults in the US suffer a Major Depressive Episode
- Most cases of Major Depressive Disorder do not remit after treatment with any current antidepressant
- Most cases of Major Depressive Disorder are classified as “treatment resistant,” i.e. failing at least two adequate trials of antidepressants.
- There are now 57 clinically approved antidepressants. Each takes weeks to take effect, with numerous side-effects, and requiring daily use for months

Better Understanding the Problem: “What is Mood?”

- My neighbor is a hand surgeon, treating disorders of the hand; I’ve been treating mood disorders for 40 years; he has no problem defining a “hand”, including an evolutionary component
- “What is Mood?”
- Aid to understanding: Wittgenstein’s theory of “language games” and choosing a preferred context (i.e., the phrase “in the mood for...”)
- Mood is defined as a predisposition for a particular type of action or inaction

The Evolutionary History of Mood

- A clearer definition of mood makes the evolutionary history of mood more evident.
- An organism's ability to internalize a predisposition for particular sorts of action or inaction began with circadian rhythms. An "internal clock" allowed the organism to predispose itself for a regularly recurring day/night environment. Before the sun arose, the organism was already in the mood for daytime activities.
- Chronobiology studies this internal ability, present in all cells for at least the past 2 billion years, and growing in complexity as organisms evolved. The systems timed became more complex. Time-frames became more complex (eg, seasonal).

MOOD DISORDERS ARE CHRONOBIOLOGICAL DISORDERS

- Major Depressive Disorder closely correlated with disrupted and desynchronized circadian rhythms, including:
 - sleep, REM sleep onset, activity level, body temperature, appetite and digestion, immune function, cortisol, thyroid-stimulating hormone, adrenalin (epinephrine), melatonin, prolactin, growth hormone, and more.
- While individual circadian rhythms are often disrupted in period or amplitude during a Major Depressive Episode, most typically the various circadian rhythms in depressed patients are desynchronized. In a Major Depressive Episode there is a disruption in the function of the brain's master circadian clock.
- These disrupted rhythms generally return to normal when the depression remits.

MOOD DISORDERS ARE CHRONOBIOLOGICAL DISORDERS (cont.)

- DSM-5 Diagnostic Criteria for a Major Depressive Episode describe a chronobiologic syndrome hiding in plain sight.
- The 4 major “vegetative signs” of MDE involve behaviors with a notable circadian pattern:

sleeping, wakefulness, activity level, feeding;

Associated chronobiological factors don't necessarily imply a chronobiological etiology of the disease...

- However, 2 validated chronobiological interventions do cause remission of a depressive episode: Light therapy, Early-wakening therapy, (plus ECT?)

notably, If these interventions work, they work quickly;

THE BODY'S "MASTER CLOCK": THE SUPRACHIASMATIC NUCLEUS IN THE BRAIN

- Paired nuclei each 10,000 neurons, anterior to hypothalamus, atop the optic chiasm; receptors for monoamines, and neural connections to monoaminergic centers
- 24 hour, 11 minute period, designed for "Zeitgebers" to reset to Time 0:00 each sunrise 24 hours later, to adapt to the changing daylight lengths
- A master clock designed to keep time, to be reset regularly, and to synchronize all slave clocks
- Terminology: "clock", a "time-piece", with kinetic functions to measure and control the rates of processes
- Heavy water among first substances found able to penetrate the SCN

HEAVY WATER: A TRULY NOVEL ANTIDEPRESSANT CANDIDATE

- Heavy water does not target any particular neurotransmitter or group of neurotransmitters
- Rather, it targets the clock that controls and synchronizes all the neurotransmitters and hormones that underlie the expression of “mood.”

HEAVY WATER: THE PROTOTYPE CHRONOBIOLOGICALLY ACTIVE CHEMICAL

- When water (H_2O) has the common “protium” isotope of hydrogen replaced by the heavier “deuterium” isotope of hydrogen, it is called “heavy water” (D_2O).
- Deuterium isotope not radioactive; it is naturally occurring; you have 5g heavy water in you now
- The deuterium isotope has essentially the same chemical reactions as the main hydrogen isotope protium, except these reactions occur at least 2-3 times more slowly; the “Kinetic isotope effect”
- For over 50 years, Heavy water has been shown to slow circadian rhythms in all species studied.
- Take home fact: D_2O produces a rapid, selective, kinetic effect on a kinetic device (SCN “Master Clock”)

SAFETY AND SIDE EFFECTS OF HEAVY WATER

- Over 80 years of studies on deuterium oxide have clearly delineated its safety profile for many species, including humans.
- Replacing 1% total body water with D₂O safe long-term for humans; 15% is safe for rats; 100% is safe for some algae
- 15% D₂O replacement can cause acute toxicity in humans
- Ratio of toxic dose to the safe, therapeutic dose (Therapeutic Index) is 15. (TI of Lithium=3)
- A heavy water dose of 450 ml (0.5 liter, 2 cups) will increase body heavy water concentration to 1%.
- Acute Dose-limiting SE: motion sickness; dose-dependent: >80 ml; prophylaxis with scopolamine

WILL PULSE OF HEAVY WATER RESET/RESYNCH DESYNCHRONIZED CIRCADIAN RHYTHMS?

- Analogous example: When multiple complex and interacting apps in your computer become desynchronized and uncoordinated, you do a reset to restart all systems together again
- Hypothesis (restated): Desynchronized circadian rhythms a major etiological factor in at least some forms of MDD
- NB: Master Clock in SCN “designed” to be reset; we are assisting and amplifying a natural process
- NB: Early Wakening treatment achieves temporary reset
- Rx: Pulse of Heavy Water synergized with this Early-Wakening reset zeitgeber to re-establish synchrony through the augmented reset

A FALSIFIABLE EXPERIMENTAL HYPOTHESIS

- A safe and efficacious single dose of deuterium oxide will reset/resynch the disordered circadian rhythms underlying a Major Depressive Episode and produce a rapid remission of the MDE.
- Efficacious dose: A dose of D_2O sufficient to increase D_2O concentration in mammals to 1% (a 100-fold increase in natural concentration) is sufficient to alter circadian rhythms.

Heavy Water Antidepressant: Trial in an animal model of depression

- Rat Forced Swim Test; high validity in predicting antidepressant effectiveness in human clinical trials
- Test completed at UCLA Behavioral Testing Core laboratory
- Rats given heavy water did 25% better than fluoxetine active control cohort, which performed as expected on serotonergic agent
- However, control group unusually active, did as well as active control, so technically a “failed experiment”

Proposed Clinical Trial Design

Diagnose Major Depressive Disorder; quantify symptom severity (eg Ham-D)

Administer a heavy water single-day dosage of 240-400ml, in 80ml aliquots given q 2h x3-5.

NB: Above protocol identical to those approved and done without significant side effect at Mass General Brigham 2017, UC-Berkeley 2003, and UCSF Medical 2002 (ref. 1-3)

Give heavy water on same day as early wakening done.

Repeat Ham-D in 1 week, 5 weeks.