A CHRONOBIOLOGIC MULTISTAGE INTERVENTION FOR THE TREATMENT OF DEPRESSION: A PILOT STUDY

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IDENTIFYING THE NEEDS

DEPRESSION

16.2% life prevalence, 30 million Americans,

WHO: second leading cause of disability worldwide by 2020,twice as many females,

15% suicide,

burden 70 B$ per year,

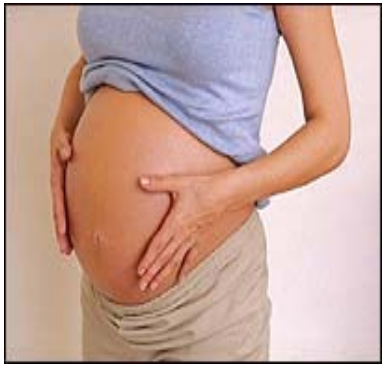
>*70% untreated*!

→ NEED 1:

TREATING THE UNTREATED DEPRESSION (**70%**)

SPECIFIC NEEDS: WOMEN, CHILDREN, OLD

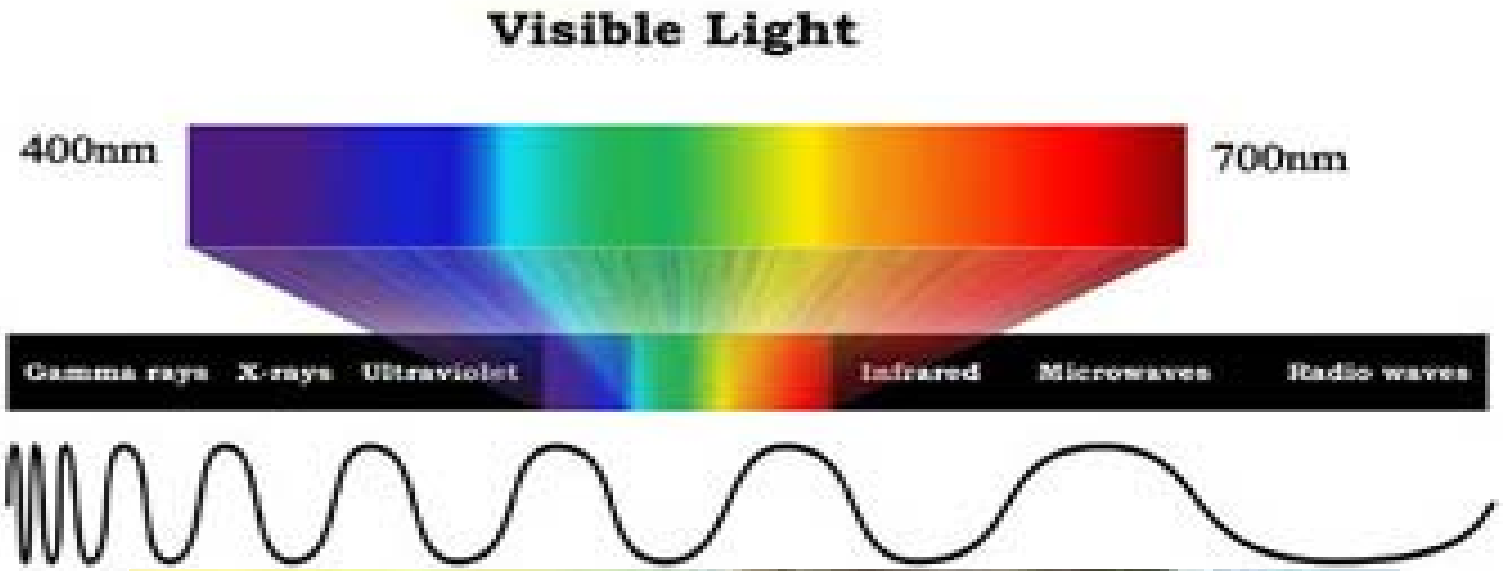
5-10% of pregnant women, medication *risky for fetus*, lactation after birth. Young & old risk



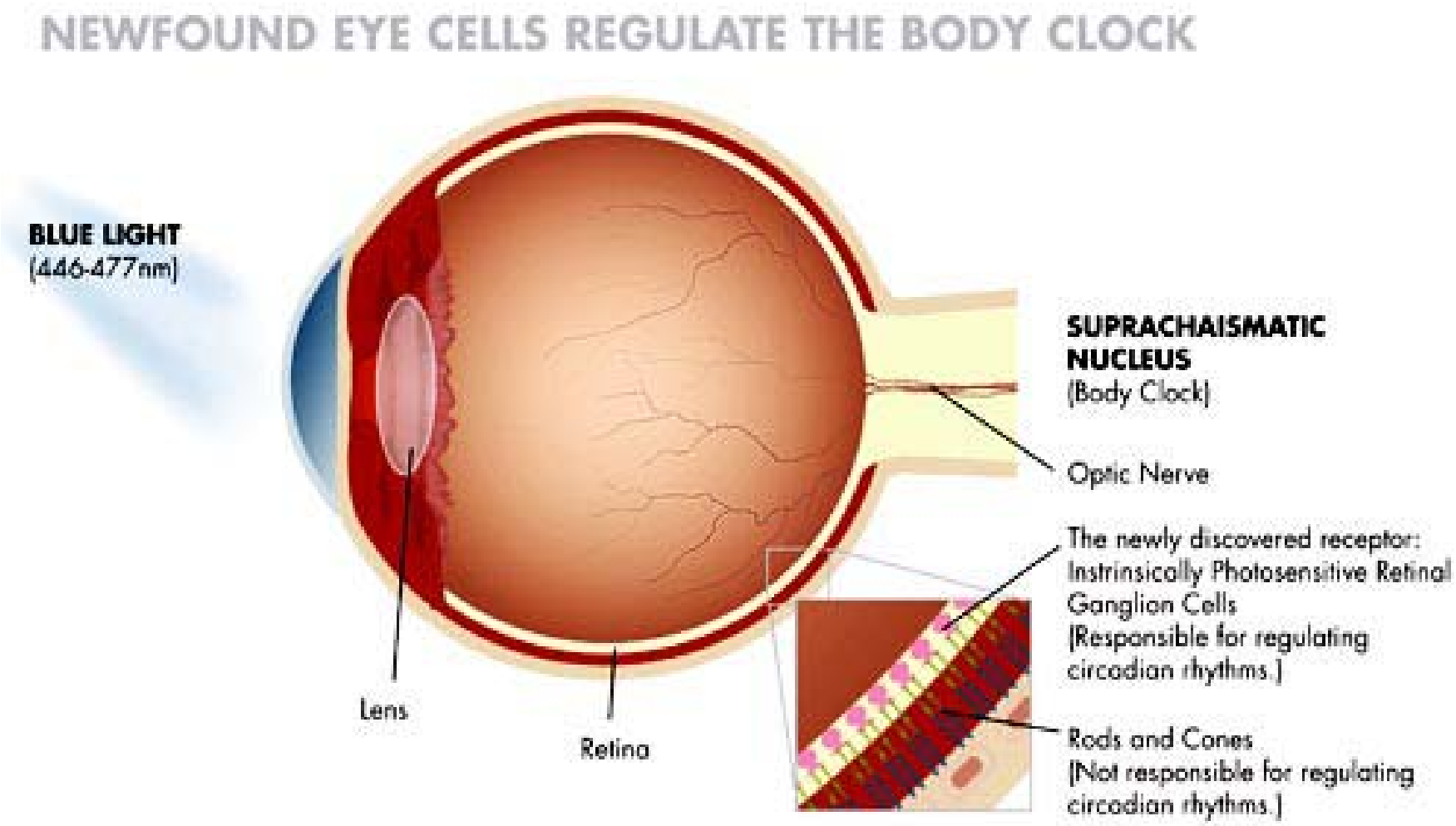
NEED 2:

→ SAFE TREATMENTS FOR PREGNANT AND LACTATING WOMEN, CHILDREN AND OLD

The “biologic clock”

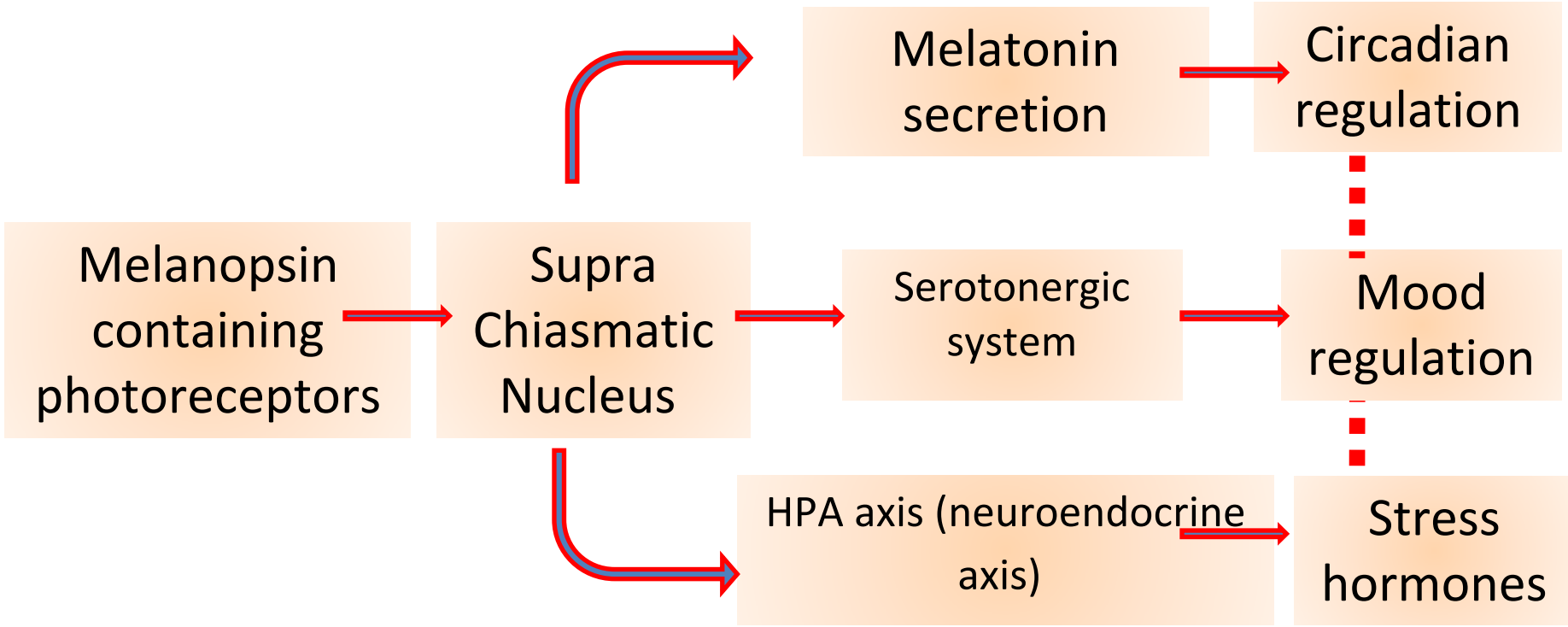


Short-medium wavelengths (blue and green) light



Chronobiology

- …Assumes connection between light exposure, circadian rhythms and mood



Chronobiologic Multistage Intervention (CMI)

4 nights treatment

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Research report

A multistage chronobiologic intervention for the treatment of depression: A pilot study

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ABSTRACT

Background: Most antidepressant medications in current use have several disadvantages: a delayed therapeutic effect, side effects, stigmatization and concerns about safety for the developing fetus during pregnancy. Several chronobiologic techniques which are free of these disadvantages were proposed as an alternative. The current article reports the design and the initial outcome results of a new chronobiologic multistage intervention (CMI) that is comprised of the following techniques: (i) partial sleep deprivation during the second half of the night (wake therapy – WT), (ii) medium (green) wavelength light in combination with dawn simulation (DS), (iii) bright light therapy (BLT), and (iv) sleep phase advance (SPA).

Methods: The study was conducted as a set of 12 single-case designs with moderate-to-severe depressive volunteering patients. Depression, anxiety and tension measurements were taken on a daily basis beginning with a baseline measurement (T0), followed by a set of four consecutive morning measurements during the therapeutic intervention (T1–T4),and with a final measurement carried out at the end of 4 weeks of follow-up (T5).

Results: A clinically significant rapid improvement of the depressive symptoms was demonstrated and maintained for at least 4 weeks after the end of the intervention. No dropouts or compliance difficulties were observed. Patient satisfaction was high, and other than having to sleep for four nights at the Research and Development Unit, participants were not inconvenienced by the nature of the therapeutic design. Sleepiness in the late afternoon hours was reported by several of the participants, but did not reach a level that interfered with their ability to function. Levels of tension did not show a consistent improvement along the intervention procedure and were not maintained in follow-up. There was some unexpected improvement in the level of anxiety that persisted at follow-up. This latter finding requires further validation by additional studies.

Conclusions: These initial findings showed the procedure to be effective and well tolerated. It affords many advantages, such as the achievement of a rapid response, no extinction of the therapeutic effect after 4 weeks of follow-up, safety, high patient compliance and cost effectiveness. These encouraging results warrant validation in further randomized controlled clinical trials.

1. Introduction

One of the major disadvantages of most antidepressant medications in current use is a delayed therapeutic effect (National Institute for Clinical Excellence, 2004; Anderson et al., 2000). This period of delay was suggested as being a risk for early dropout (Nemeroff, 2003) and increased suicidal tendency, especially among children and adolescents (US Food and Drug Administration, 2004; Akiskal and Benazzi, 2006). Other disadvantages of pharmacotherapeutic agents are associated with its side effects and drug–drug interactions (Nemeroff et al., 2007), tolerability (Papakostas, 2008), and stigmatization (Interian et al., 2007). Moreover, the treatment of depression with the aid of antidepressant medications during pregnancy and the postpartum period raises unique concerns about safety for the developing fetus as well as the infant (Pearlstein, 2008).

Several chronobiologic techniques were proposed as interventional modalities with the purpose of obtaining a rapid, antidepressive effect free of side effects and the other above-

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First night aims:

1. Resetting the circadian cycle.
2. Prolonged wake therapy.
3. Sleep phase advance.

First night protocol

21:00 - No sleeping instructions

02:30 - Gradual increase of white light (0-400 lx) (dawn simulation) (30 minutes).

03:00 - Green light (400 lx) (30 green - 525 nm) (2.5 hours).

05:30 - BLT (5,000 lx) (30 minutes).

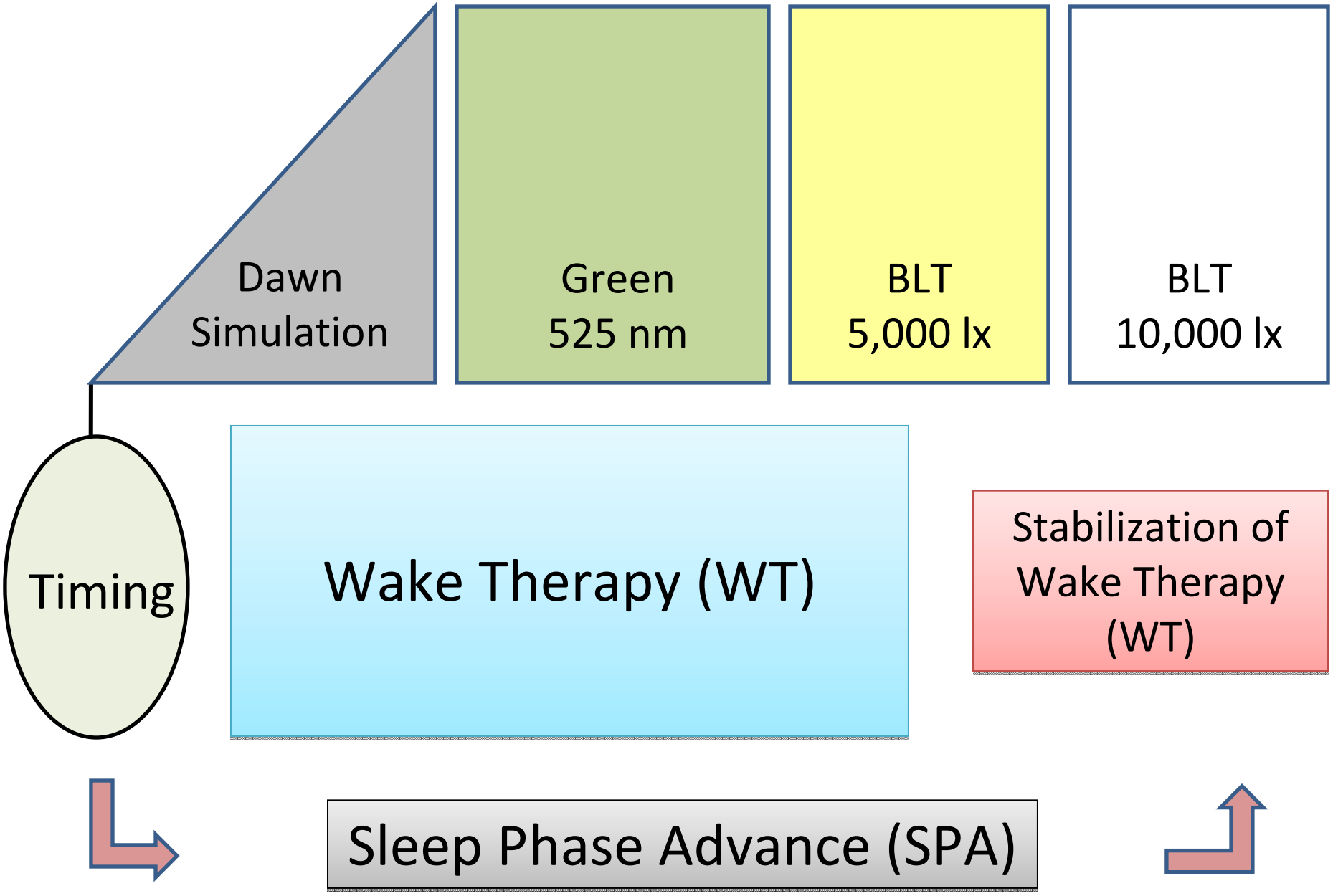
06:00 - BLT (10,000 lx) (30 minutes).

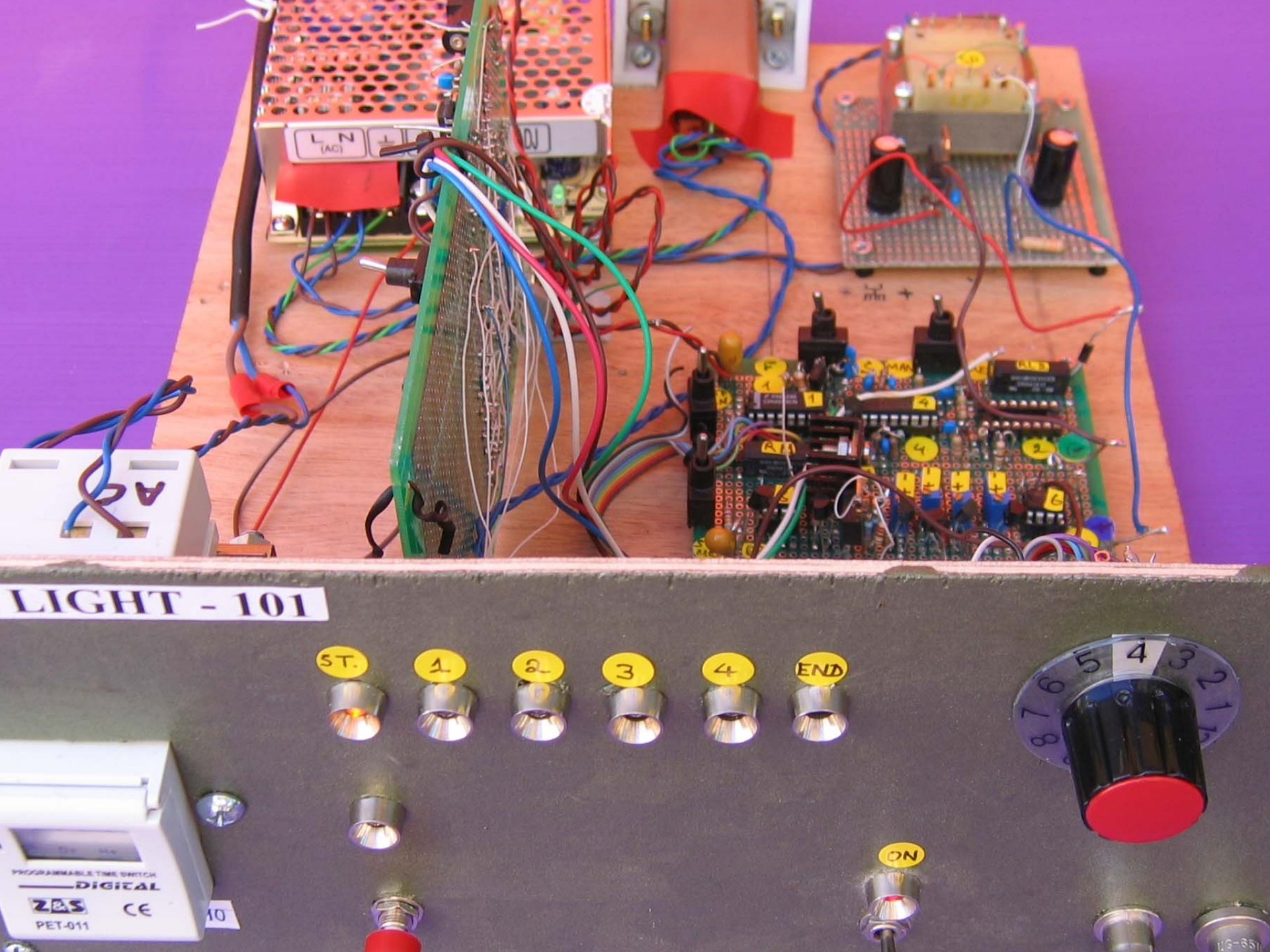
Second-fourth nights aims:

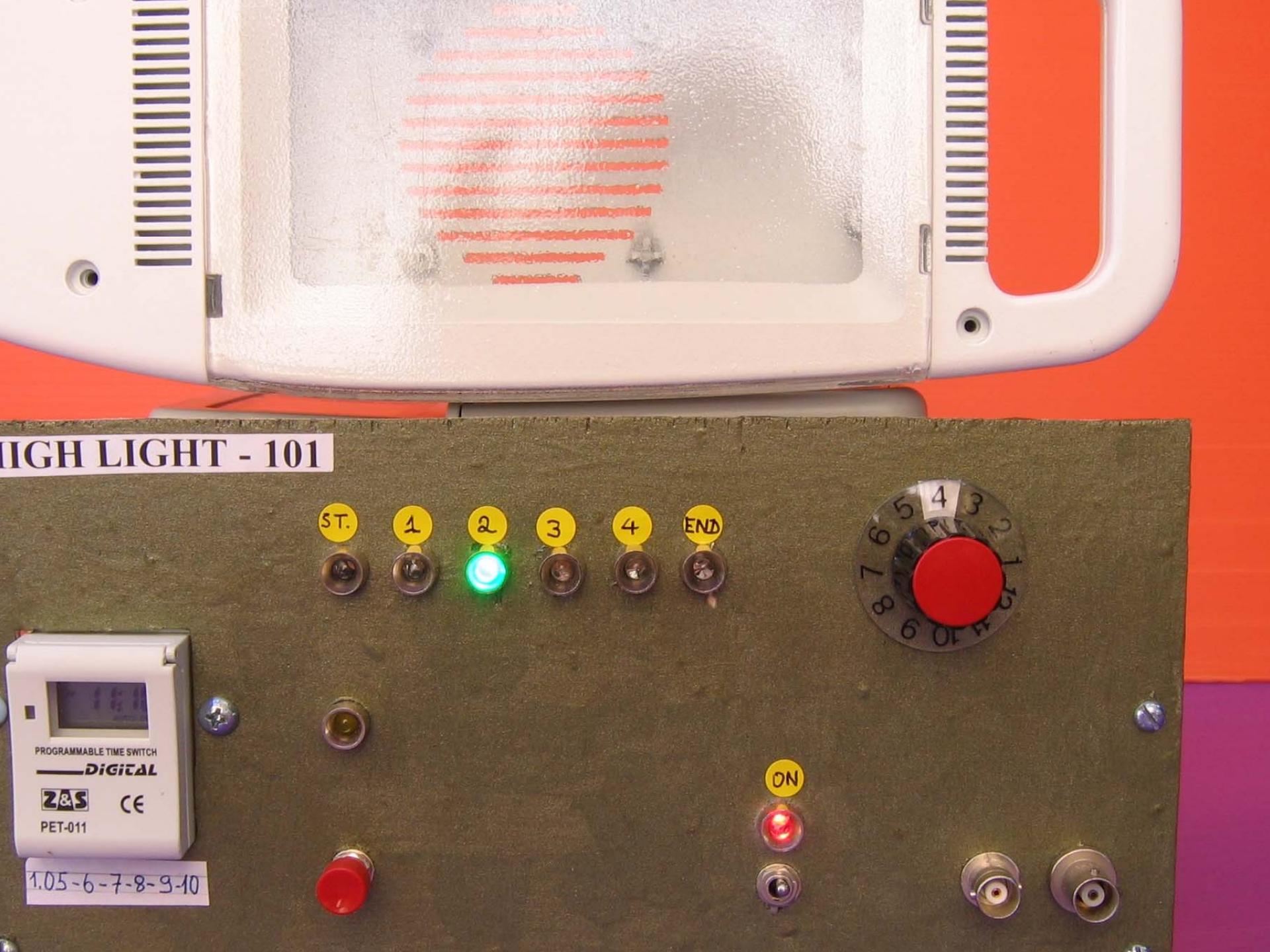
1. Sleep phase advance.
2. Stabilization of the effect of Wake Therapy.
3. Short late-night sleep deprivation.

Second-fourth nights protocol:

- 19:00 - Patient is requested to go to sleep earlier.
- 03:00 - Dawn simulation (30 minutes).
- 03:30 - Green light (2 hours).
- 05:30 - 5,000 lx exposure (30 minutes).
- 06:00 - 10,000 lx exposure (30 minutes).


Dawn
Simulation
Green
525 nm
BLT
5,000 lx
BLT
10,000 lx
Timing
Wake Therapy (WT)
Stabilization of
Wake Therapy
(WT)
Sleep Phase Advance (SPA)


LIGHT - 101
ST.
1
2
3
4
END
ON
PROGRAMMABLE TIME SWITCH
DIGITAL
PET-011


IGH LIGHT - 101
ST.
1
2
3
4
END
PROGRAMMABLE TIME SWITCH
DiGiTAL
Z&S
CE
PET-011
1.05-6-7-8-9-10
ON

Outcomes Evaluation

Study design:

- 12 single-case designs
- Volunteers
- No control-group

Inclusion criteria:

- At least four of the main criteria symptoms which are listed for a depressive episode diagnosis (F32) in the ICD-10.
- A signed informed consent.

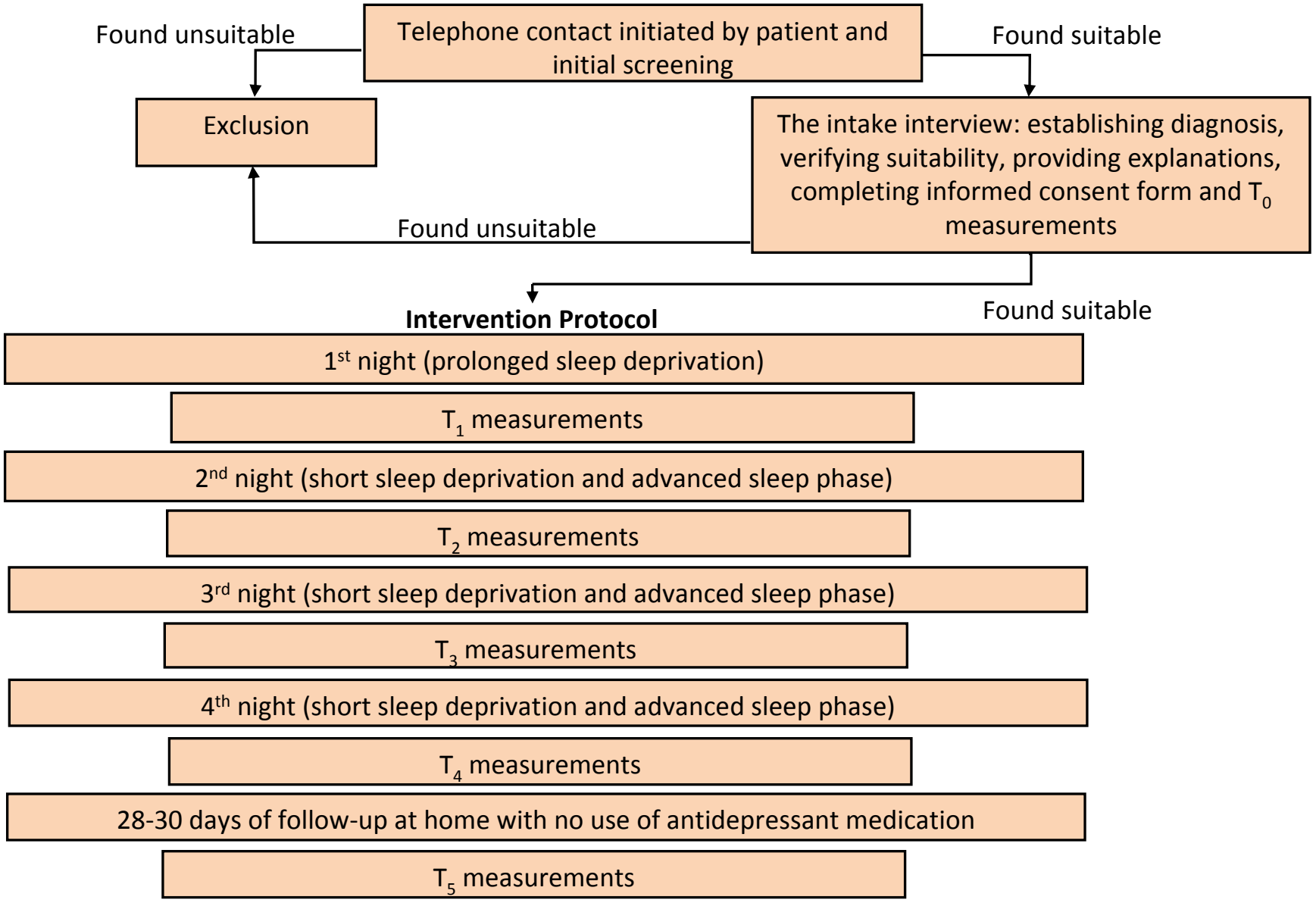
Exclusion criteria:

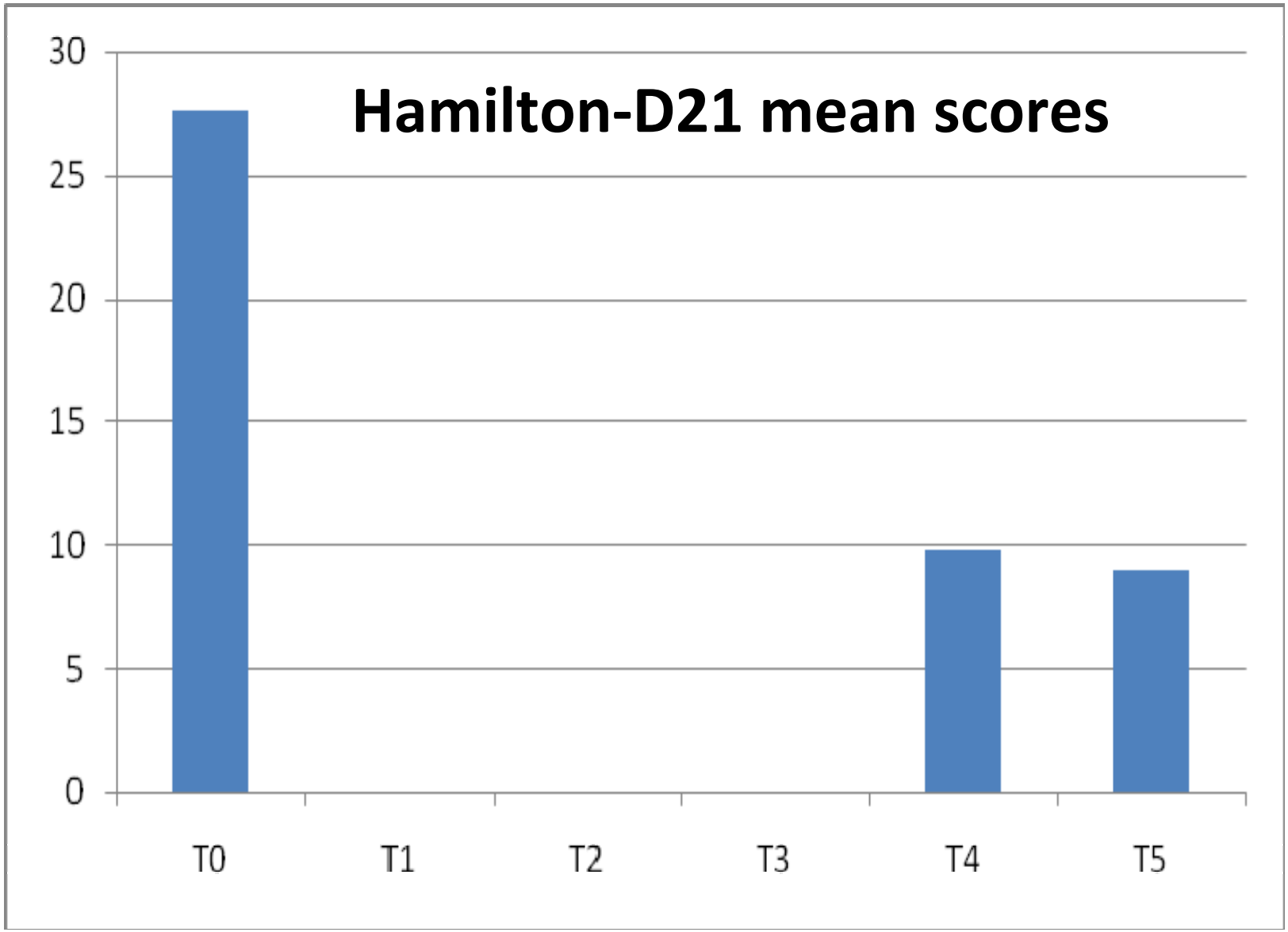
- The use of anti-depressant agents for at least 5 weeks prior to the trial.
- Retinal disease and/or cataract.
- current suicidal thoughts or past suicidal history.
- A history of psychotic, bipolar affective disorders and alcohol or substance abuse.

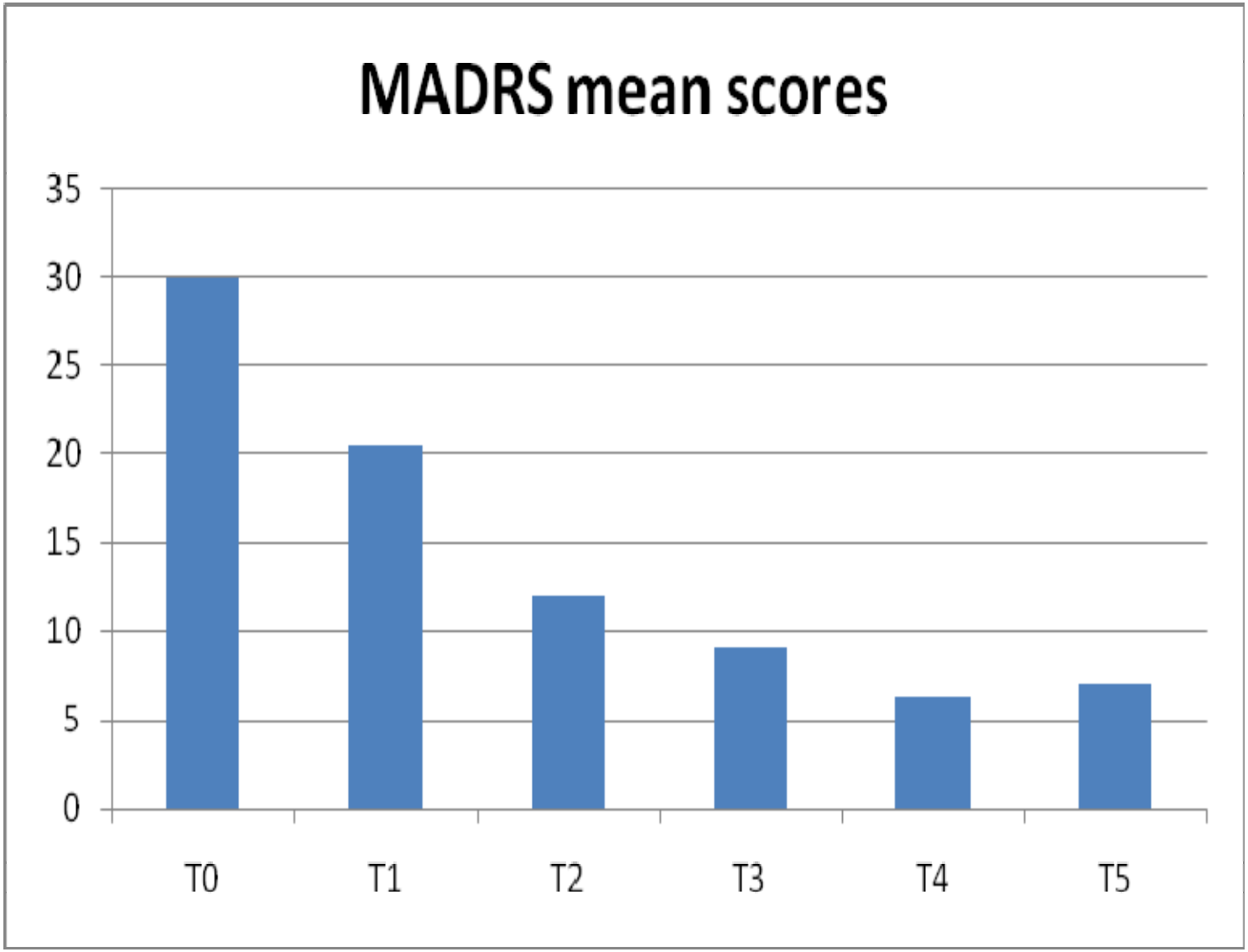
Measurements:

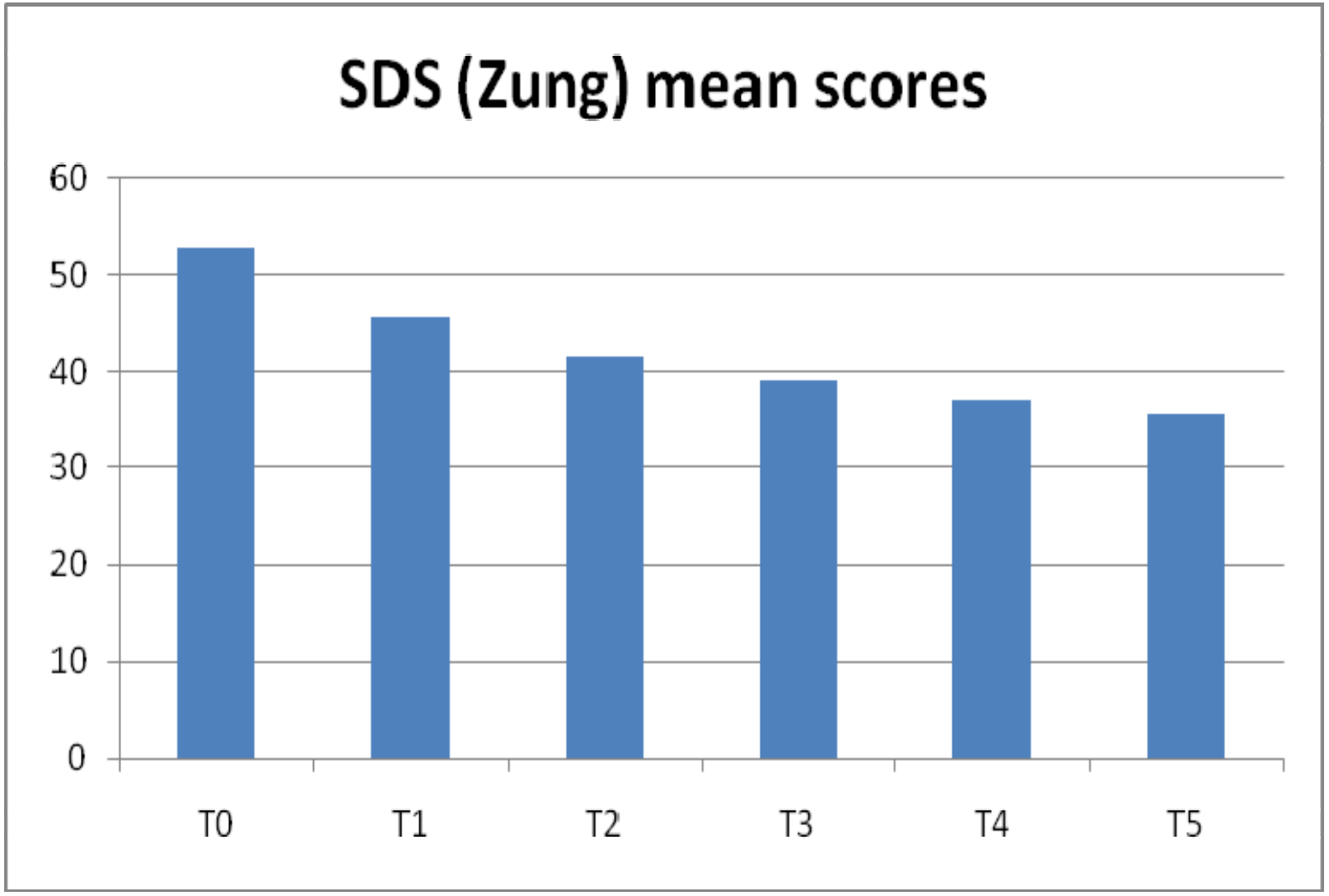
- HAM-D 21
- MADRS
- Zung self-rating scale
- Depression VAS
- Anxiety VAS
- Tension VAS

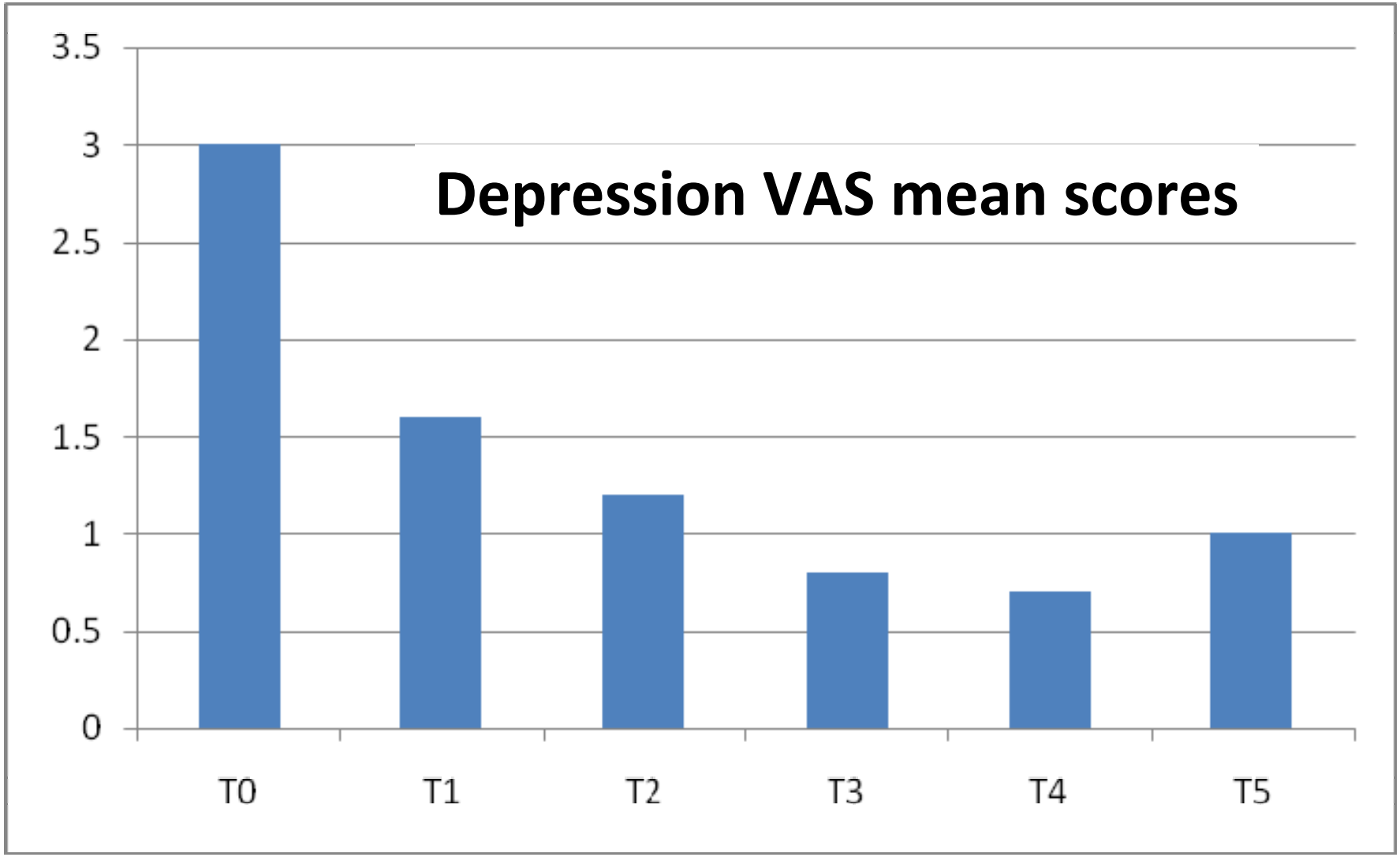
Figure1. Illustration of the course of the study

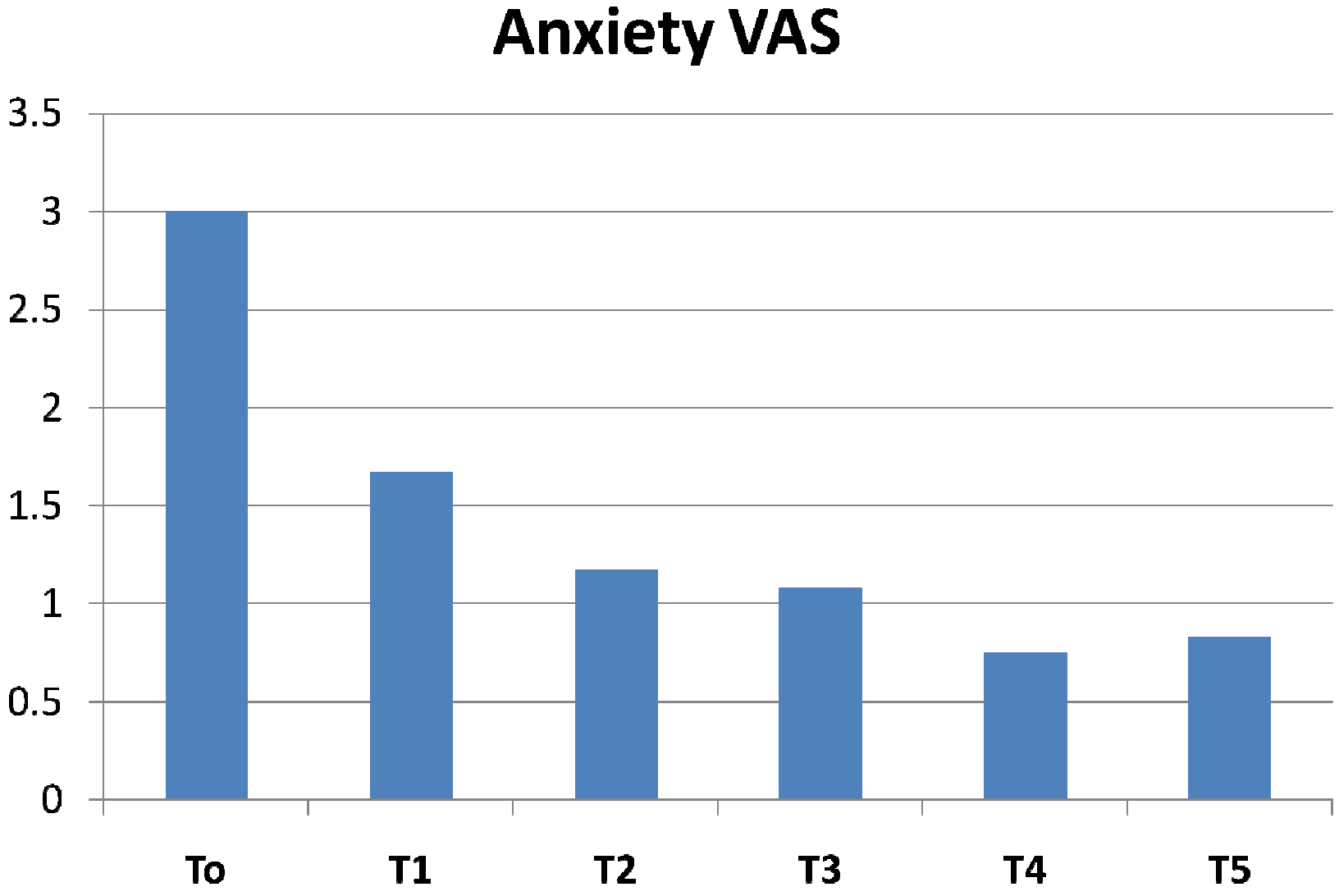


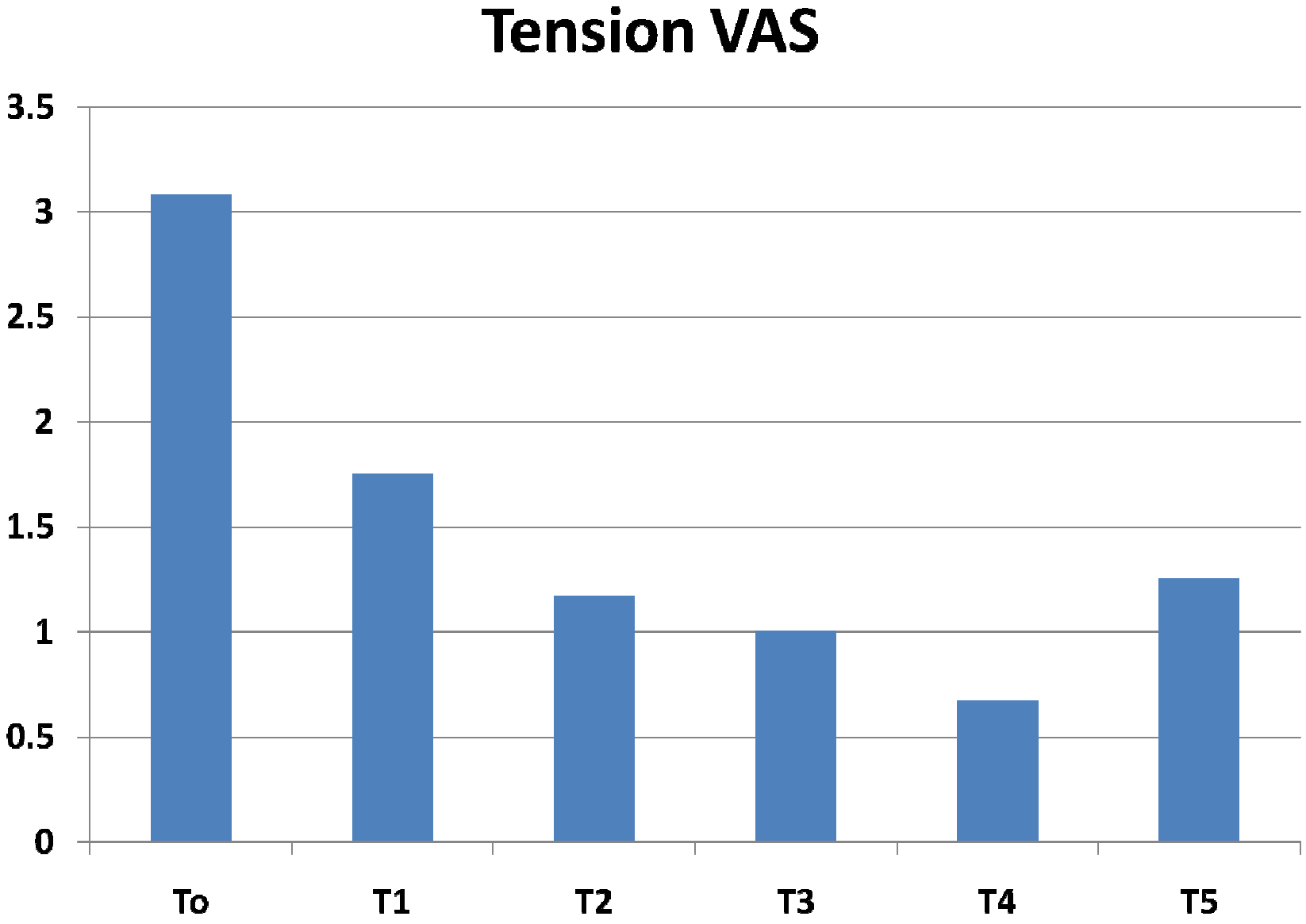

Hamilton-D21 mean scores
30
25
20
15
10
5
0
T0
T1
T2
T3
T4
T5


MADRS mean scores
35
30
25
20
15
10
5
0
T0
T1
T2
T3
T4
T5


SDS (Zung) mean scores
60
50
40
30
20
10
0
T0
T1
T2
T3
T4
T5


Depression VAS mean scores
3.5
3
2.5
2
1.5
1
0.5
0
T0
T1
T2
T3
T4
T5


Anxiety VAS
3.5
3
2.5
2
1.5
1
0.5
0
To
T1
T2
T3
T4
T5


Tension VAS
3.5
3
2.5
2
1.5
1
0.5
0
To
T1
T2
T3
T4
T5

Conclusions

- CMI definitely achieves clinically impressive results.
- CMI is based on distinct components which had been proved to be effective in previous studies. But the combination of all these in one protocol seems to make it even more effective.
- There are few and rare known side-effects or counter-indications.
- There is sufficient reason to further conduct a larger single blind three arms comparative study: CMI versus placebo & waiting list.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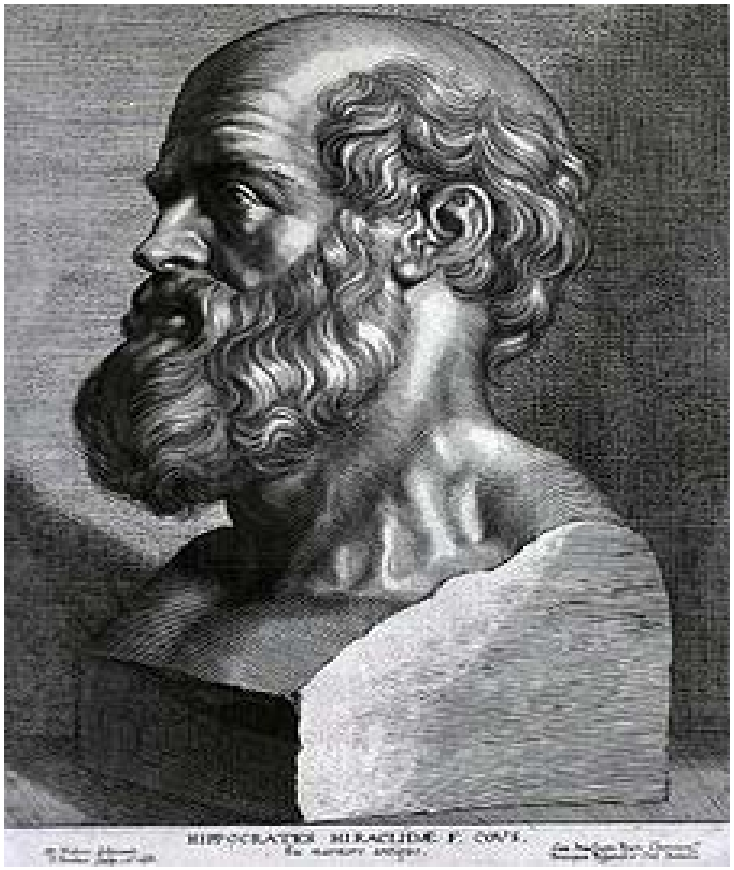

“Vis Medicatrix Naturae“

Hippocrates

460-370 BC