The Internal Family System Model: Treating the Long-Term Effects of Trauma

Pre-Conference Workshop
28th Annual International Trauma Conference
2017
Boston

Richard C. Schwartz, PhD and Michael Mithoefer, MD

Michael Mithoefer's Research sponsored by
The Multidisciplinary Association for Psychedelic Studies
Santa Cruz, CA

Outline

History of MDMA

Why study MDMA-assisted Therapy for PTSD

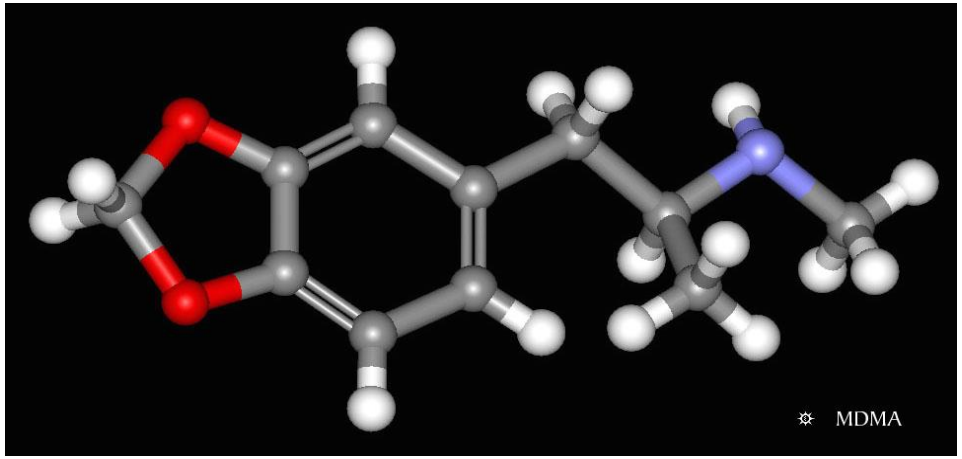
Clinical Trials of MDMA-assisted Psychotherapy for PTSD

Video clips from MDMA-assisted sessions

Discussion

MDMA

Ring-substituted
phenylisopropylamine
derivative



http://www.erowid.org/chemicals/mdma/mdma_chemistry.shtml

Patented in 1914 by Merck
now off-patent

"**Entactogen**"
closeness to others
empathy
well being
insightfulness
less perceived loss of control than classical psychedelics

Legal Therapeutic Use pre 1985 Scheduling

Greer and Tolbert (1986)

clinical experience and 2 year follow-up of 29 patients after MDMA-assisted psychotherapy

Grinspoon and Bakalar (1986)

review of therapeutic use with numerous individual case reports

Samuel Widmer, MD, Peter Gasser, MD, et.al

Swiss Medical Society for Psycholytic Therapy permission from the Swiss Ministry of Health to administer MDMA to patients from 1988 to 1993. 171 patients received MDMA no significant adverse effects reported

Early 1980s Estimated 4000 Therapists Administering MDMA

MDMA Scheduling

1976 - Alexander Shulgin synthesized & introduced it to therapists as a therapeutic tool

1978 – First published report of human administration
Shulgin and Nichols

Early 1980s - Increased recreational use, “Ecstasy”

July 1 1985 - Emergency temporary Schedule I by DEA

May 1986 - After hearings judge recommended Schedule III

March 1988 - After appeals DEA administrator overruled recommendations from hearings and placed MDMA in Schedule I “permanently”

Resurgence of MDMA Clinical Research

November 2000 - our first Phase II Protocol Approved by FDA

February 2004 - DEA Approval

April 2004 – First Participant Enrolled

As of 2016 Six Phase II Clinical Trials
of MDMA-assisted Psychotherapy for PTSD completed

WHY DID WE PURSUE THIS?

Existing PTSD Treatments

Pharmaceuticals can help with symptoms

- Not definitive treatment
- Many drugs have serious side effects

Existing PTSD Treatments

Psychotherapy is the definitive treatment

≤ 50% of people respond to existing therapies

Many trauma therapies have a narrow focus
on the trauma -

This isn't true of IFS!

Can a Drug Improve Response to Therapy?

Three Fundamental Avenues of Healing Trauma

1) Top down

Talking
Reconnecting with others
Allowing ourselves to know and understand what is going on with us while processing memories of the trauma

2) Medicines and other technologies

shutting down inappropriate alarm reactions
changing the way the brain organizes information

3) Bottom up

Allowing the body to have experiences that deeply and viscerally contradict the helplessness, rage or collapse that result from trauma

The Body Keeps the Score, Bessel van der Kolk

Most Trauma Therapies do not Include all Three

Psychotherapy for Trauma Needs to Include:

A Catalyst

processing trauma, reconnecting with others

Brain changes

Modulation of fear reactions

Less constrained “repertoire of functional connectivity”

Carhart-Harris et al. 2014

Affirming Experiences

“deep and visceral”, compassion for self and others

Broader Scope

The complex realities of trauma, life, relationships

There is Evidence that MDMA Can Address these Needs

Psychotherapy for Trauma Needs to Include:

A Catalyst

processing trauma, reconnecting with others

Brain changes

Modulation of fear reactions

Less constrained “repertoire of functional connectivity”

Carhart-Harris et al. 2014

Affirming Experiences

deep and visceral, compassion for self and others

Broader Scope

The complex realities of trauma, life, relationships

MDMA Pharmacology

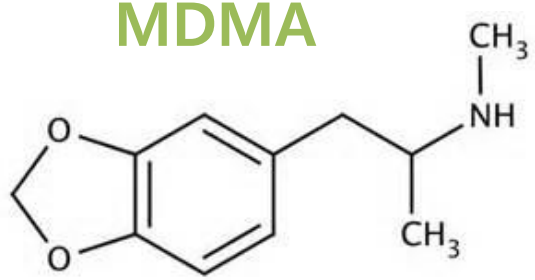
Increases release of:

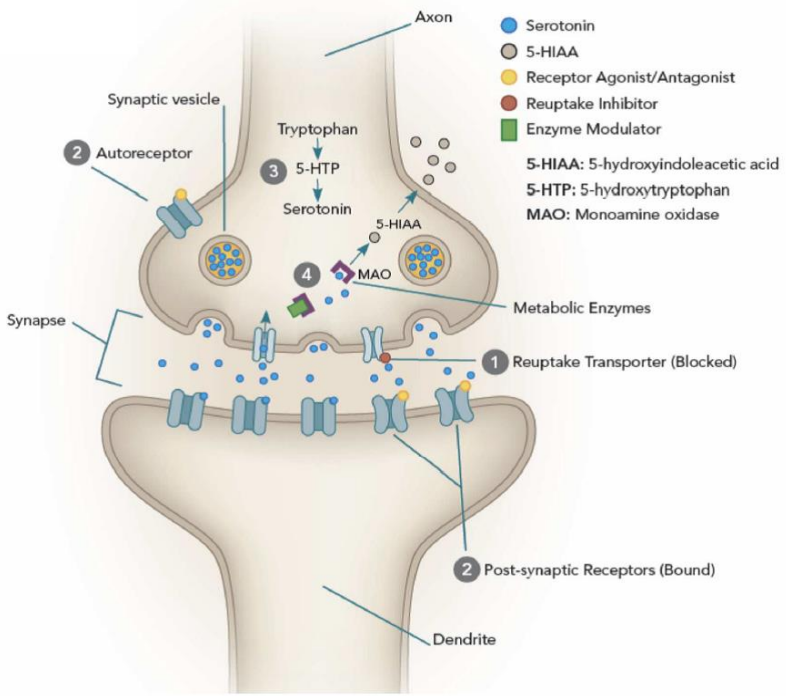
serotonin (5-HT)
norepinephrine (NE)
dopamine (DA)

Enhances release of hormones:

oxytocin
prolactin
vasopressin
cortisol

MDMA





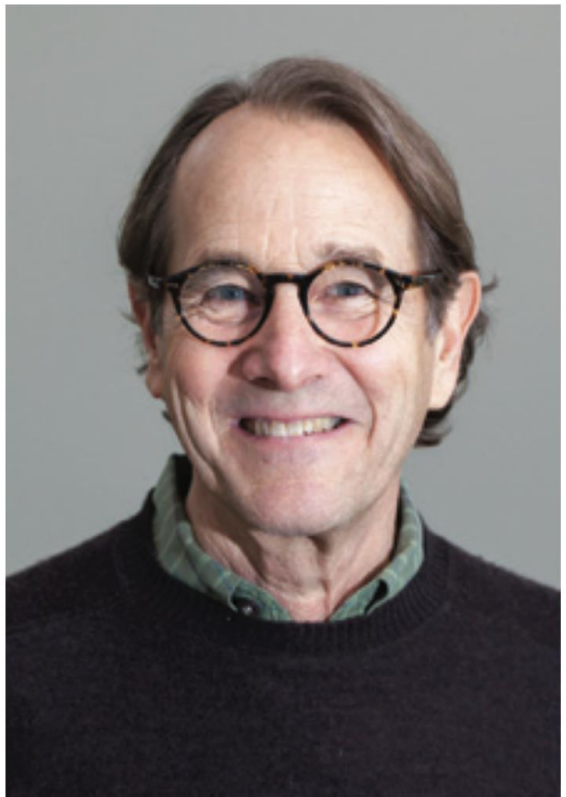
MDMA Pharmacology

RECEPTORS OR BRAIN REGION INVOLVED	MDMA EFFECTS	HOW EFFECTS RELATE TO THE TREATMENT OF PTSD		NEURO-BIOLOGICAL CORRELATES
SEROTONIN	Reduces depression and anxiety	Provides patient with an experience of positive mood and reduced anxiety in increased engagement. (Harris 2002, Hysek 2013).		Release of pre-synaptic 5-hydroxytryptamine at 5-HT_{1A} and 5-HT_{1B} receptors. (Brunner 1997)
	Stimulates alterations in the perceptions of meaning.	Opportunity to see old problems in a new light.		Increased activity at the 5-HT_{2A} receptors (Nash 1994)
DOPAMINE AND NOR-EPINEPHRINE	Raises levels of arousal.	Stimulating effect increases motivation to engage in therapy	Optimum Level of Arousal (Foa 2009)	Release of dopamine and noradrenaline (Cozzi 1999)
ALPHA-2 ADRENO-CEPTORS	Increases relaxation.	Reduces hypervigilance associated with PTSD		Increased alpha 2-adrenoceptor activity. (Lavelle 1999)
HORMONAL EFFECTS	Improves fear extinction learning.	Allows reflection on traumatic memories during psychotherapy without being overwhelmed.		Release of noradrenaline and cortisol
	Increases emotional attachment and feelings of trust and empathy.	Improved relationship between patient and therapist. Capacity to reflect on traumatic memories.		Multiple factors, including release of oxytocin. (Thompson 2007)
	More likely to use words relating to friendship, and intimacy	Generate discussion about wider aspects of the patient's social and emotional relationships.		
	Reduced social exclusion phenomena.	Opportunity to reflect upon patients' wider social functioning.		
REGIONAL BRAIN CHANGES	Improved detection of happy faces and reduced detection of negative faces.	Enhances levels of shared empathy and pro-social functioning.		Increased PFC activation and decreased amygdala fear response. (Gamma 2000, Hysek 2012).
	Reduced subjective fear response on recall of negative memories.	Opportunity to reflect upon painful memories of trauma during psychotherapy.		Decreased cerebral blood flow in the right amygdala and hippocampus. (Carhart-Harris et al 2015)

Table One: How MDMA's Psychotherapeutic Effects Relate to its Unique Receptor Profile (Sessa 2016)

MDMA-Assisted Psychotherapy: How Different is it from Other Psychotherapy?

MICHAEL MITHOEFER, MD



"Have a big story or no story at all, but don't have a small story."

These words resonated deeply for me when I first heard them from Stan Grof over 20 years ago. They're always in the mix when I think about what we know and what we're discovering about psychological healing—even the term "psychological healing" implies a small story separating psychology from physiology, spirituality, and other possible levels of healing. In research we need to formulate and test hypotheses, which are of necessity small stories or only small parts of a much bigger story. However elegant and illuminating our hypotheses may be, there is the danger that they will become conceptual traps limiting our capacity to observe and respond to the unexpected. A comprehensive understanding of the human psyche remains elusive and is no doubt far beyond any of our limited hypotheses.

For me, doing MDMA research in a rigorous, scientific way always involves a tension between striving to understand and not needing to understand. The ongoing challenge is to balance my intention not to be attached to any story at all—to be open and receptive to unexpected discoveries when we're sitting with people in MDMA psychotherapy sessions—with the inescapable and potentially fruitful propensity of my rational mind to weave new discoveries into our evolving understanding of therapeutic

“I don’t know why they call this ecstasy!”

Psychotherapy for Trauma Needs to Include:

A Catalyst

processing trauma, reconnecting with others

Brain changes

Modulation of fear reactions

Less constrained "repertoire of functional connectivity"

Carhart-Harris et al. 2014

Affirming Experiences

deep and visceral compassion for self and others

"Emotional regulation is the critical issue in managing the effects of trauma and neglect… in order to change you need to open yourself to your inner experience…"

The Body Keeps the Score, Bessel van der Kolk

Broader Scope

The complex realities of trauma, life, relationships

Window of Tolerance

Increased sensation
Emotional reactivity
Intrusive imagery
Disorganized cognitive processing

Window of Tolerance / Optimal Arousal Zone

Numbing of emotions
Disabled cognitive processing

Adapted from Ogden P et al. *Psychiatr Clin North Am*. 2006;29(1):263-279, xi-xii

Arousal Zone in IFS Terms

Blending with frightened exiles
Firefighters

Self Energy
Courage, Compassion, Clarity

Shut Down by Protectors

MDMA in Healthy Volunteers

ELSEVIER

3,4-Methylenedioxymethamphetamine (MDMA) Modulates Cortical and Limbic Brain Activity as Measured by [$H_2{}^{15}O$]-PET in Healthy Humans

Alex Gamma, Ph.D., Alfred Buck, M.D., Thomas Berthold, Daniel Hell, M.D., and Franz X. Vollenweider, M.D.

[$H_2{}^{15}O$]-Positron Emission Tomography (PET) was used to examine regional cerebral blood flow (rCBF) after administration of a single oral dose of the serotonin realeaser and uptake inhibitor MDMA (1.7 mg/kg) or placebo to 16 MDMA-naïve subjects. Psychological changes were assessed by psychometric rating scales. MDMA produced distributed changes in regional blood flow including increases in ventromedial frontal and occipital cortex, inferior temporal lobe and cerebellum; and decreases in the motor and somatosensory cortex, temporal lobe including left amygdala, cingulate cortex, insula and thalamus. Concomitant with these changes, subjects experienced heightened mood, increased extroversion, slight derealization and mild perceptual alterations. MDMA also produced increases in blood pressure and several side effects such as jaw clenching, lack of appetite and difficulty concentrating. These results indicate that a distributed cluster of brain areas underlie the various effects of MDMA in humans. **[*Neuropsychopharmacology* 23:388–395, 2000]** *© 2000 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

KEY WORDS: *MDMA; Ecstasy; H_2O-PET; CBF; Serotonin; Human; Psychological effects*

3,4-Methylenedioxymethamphetamine (MDMA) is the major component of the widely used recreational drug "Ecstasy." In a clinical setting, MDMA produces a robust enhancement of mood and extroversion, slight derealization and a physiological response characterized by marked increases in heart rate and blood pressure (Vollenweider et al. 1998). Acute adverse effects include jaw clenching, lack of appetite, difficulty concentrating and impaired balance.

Animal studies have shown that MDMA predominantly releases serotonin via interaction with the serotonin (5-HT) transporter (Rudnick and Wall 1992; Schmidt 1987), and, to a lesser extent, also dopamine (Yamamoto and Spanos 1988). Consistent with these results, recent work in our lab demonstrated that both the psychological and physiological effects of MDMA can be attenuated by pretreatment with the selective serotonin uptake inhibitor citalopram, while the dopamine D_2 antagonist haloperidol only reduced MDMA-induced positive mood (Liechti et al. 1999; Liechti et al. unpublished observations). These results suggest that the subjective and physical response to MDMA in humans is largely dependent on the enhancement of serotonergic neurotransmission.

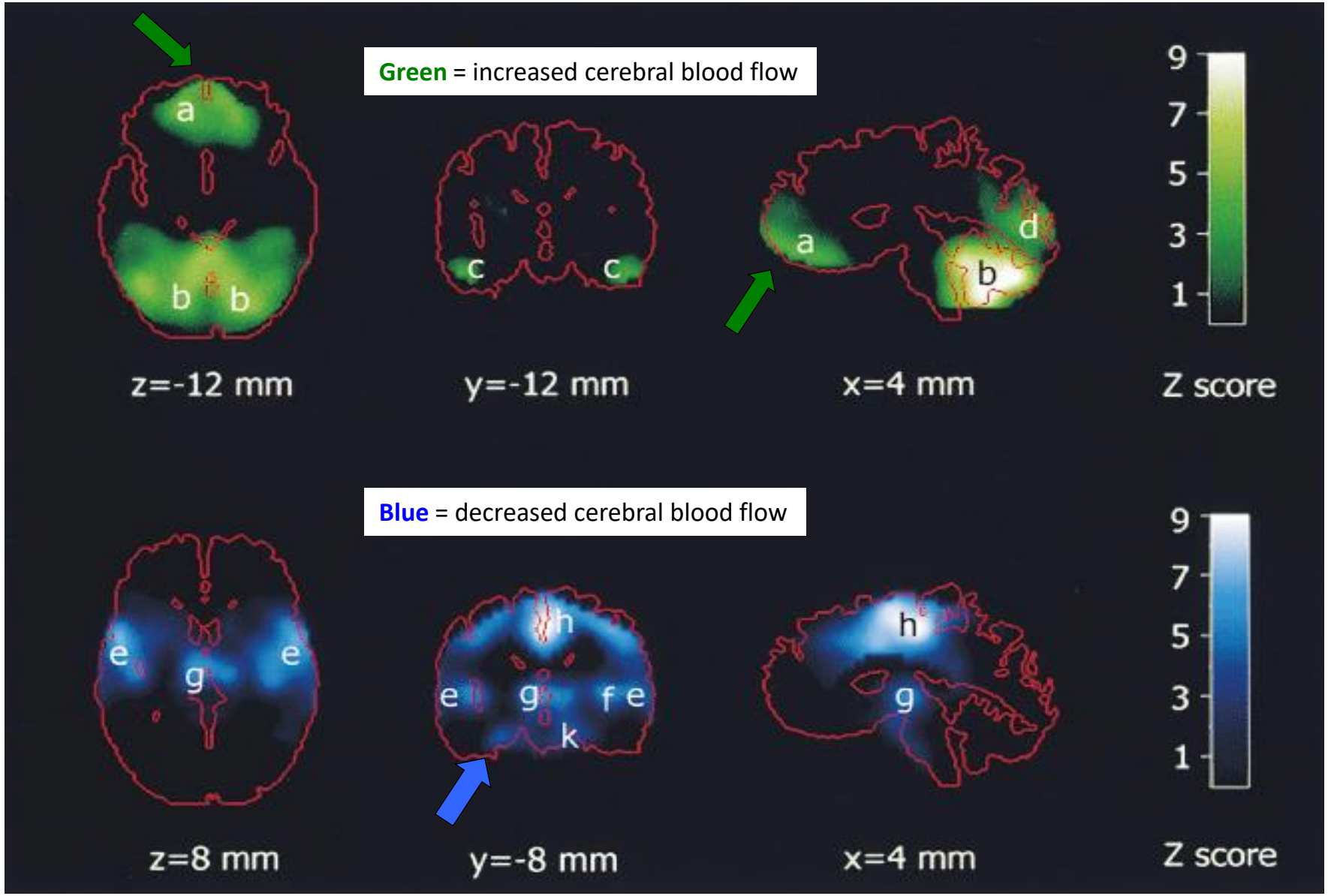
The neurophysiological basis of the various effects of

From the University Hospital of Psychiatry Zurich, PO Box 68, 8029 Zurich, Switzerland (AG, DH, FXV); University Hospital Zurich, Institute of Nuclear Medicine, Department of Medical Radiology, 8091 Zurich, Switzerland (AB, TB).
Address correspondence to: Dr. Franz X. Vollenweider, University Hospital of Psychiatry, Lenggstr. 31, 8029 Zurich, Switzerland.
Received November 23, 1999; revised March 28, 2000; accepted April 7, 2000.

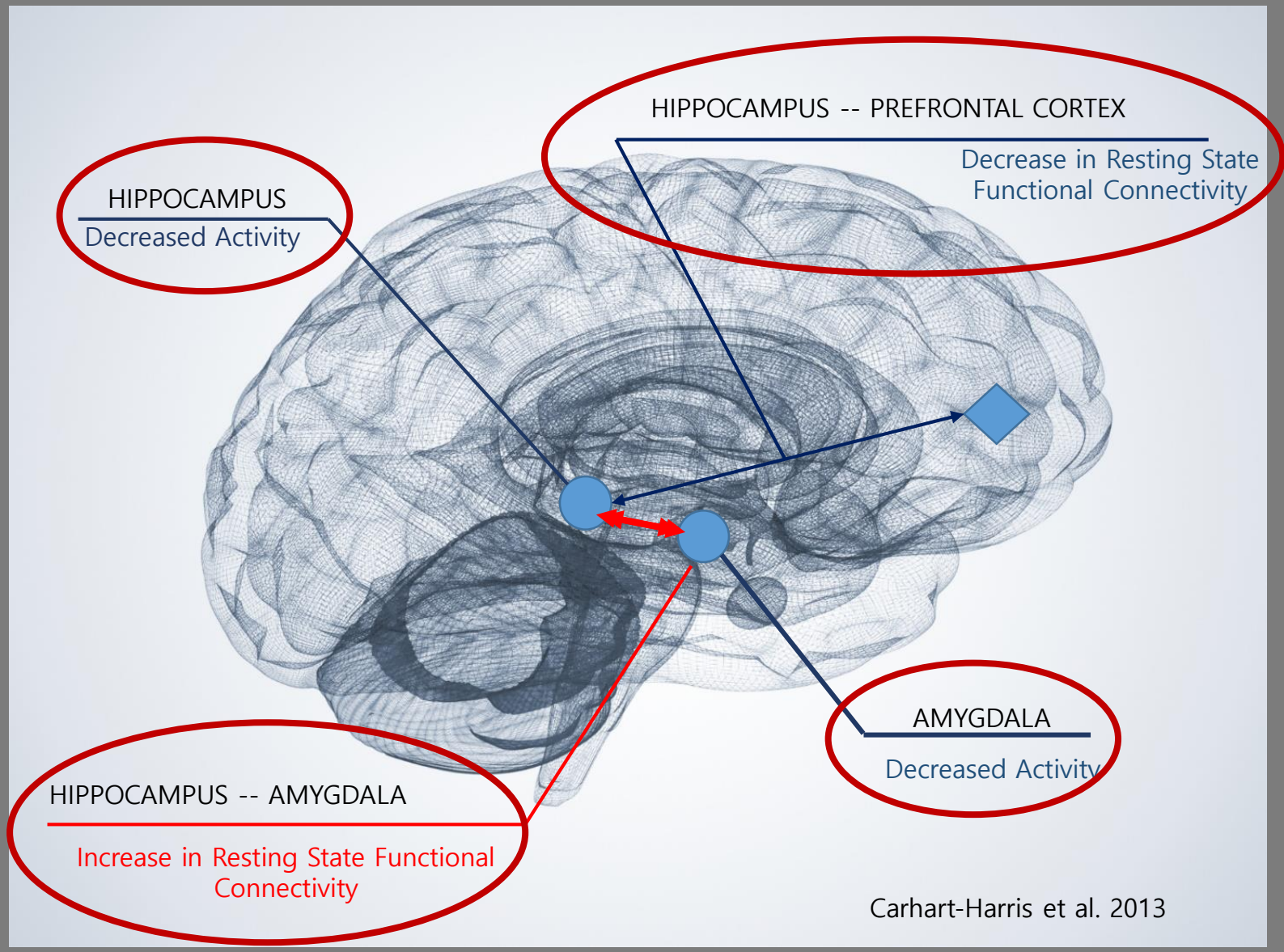
NEUROPSYCHOPHARMACOLOGY 2000–VOL. 23, NO. 4

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/00/$–see front matter
PII S0893-133X(00)00130-5


Green = increased cerebral blood flow
a
b
b
c
c
a
d
b
9
7
5
3
1
z=-12 mm
y=-12 mm
x=4 mm
Z score
Blue = decreased cerebral blood flow
e
e
g
h
e
g
f e
k
h
g
9
7
5
3
1
z=8 mm
y=-8 mm
x=4 mm
Z score

After 100 mg MDMA: changes in cerebral blood flow and resting state functional connectivity



“Maybe one of the things the drug does is let your mind relax and get out of the way because the mind is so protective about the injury.”

" It feels almost like the inner healer or the MDMA is like a maid doing spring cleaning. It's as if you thought you were cleaning before but when you got to things you didn't really want to deal with you'd just stick them in the attic. If you're going to clean the house you can't skip the stuff in the attic”

“I have respect for my emotions now…
What’s most comforting is knowing
now I can handle difficult feelings
without being overwhelmed.”

Psychotherapy for Trauma Needs to Include:

A Catalyst

processing trauma, reconnecting with others

Brain changes

Modulation of fear reactions

Less constrained “repertoire of functional connectivity”

Carhart-Harris et al. 2014

Affirming Experiences

deep and visceral, compassion for self and others

Broader Scope

The complex realities of trauma, life, relationships

“I’m a huge pile of fertilizer composting and turning into beautiful rich soil. It’s a perfect time to have rain. I’m a converter, I’m the earth, I am. Leaves, rain, even acid rain hit me, and I have a powerful ecosystem, all can be absorbed. What we’re doing here is turning compost.”

“I feel like I’m walking in a place I’ve needed to go for so long and just didn’t know how to get there. I feel like I know myself better than I ever have before. Now I know I’m a normal person. I’ve been through some bad stuff, but…those are things that happened to me, not who I am…

This is me, the medicine helps, but this is in me.”

“I got a glimpse of more of what I’m capable of growing into…I’m motivated to keep practicing openness until it gets more developed …”

Psychotherapy for Trauma Needs to Include:

A Catalyst

processing trauma, reconnecting with others

Brain changes

Modulation of fear reactions

Less constrained “repertoire of functional connectivity”

Carhart-Harris et al. 2014

Affirming Experiences

deep and visceral, compassion for self and others

Broader Scope

The complex realities of trauma, life, relationships

“Before my treatment, PTSD was an island on which I was stranded. I now attend weddings, birthdays, church, and even go to the grocery store without panic, finally feeling connected to my life and my family again.”

Ed Thompson

Firefighter and MAPS Study Participant, MP-8

“Traumatized human beings recover in the context of relationships:…
Recovery from trauma involves reconnecting with our fellow human beings”

The Body Keeps the Score, Bessel van der Kolk

Therapist:

“Are you feeling connected to us?”

Veteran:

“Yeah, yeah, if I didn’t feel connected to you, I wouldn’t be able to talk about these things”

Prosocial effects of MDMA

Well documented, but not completely understood

Harriet de Wit, Ph.D.

MDMA has “unique prosocial effects. It enhances feelings of social closeness and may dampen reactivity to negative social stimuli, such as social threat and rejection.”

Kim Kuypers, Ph.D.

Neurobiology Underlying the Prosocial Effects of MDMA

MDMA “induces facilitation of social behavior i.e.
increased feeling of closeness to others, empathy, and euphoria”

Not as simple as oxytocin and serotonin

"Here, we argue for the importance of using all the available tools of modern basic and clinical neuroscience research to map MDMA's mechanism of action in the brain...The world's populations need more compassion and empathy for one another. The study of MDMA provides one small but potentially important step toward reaching that goal."

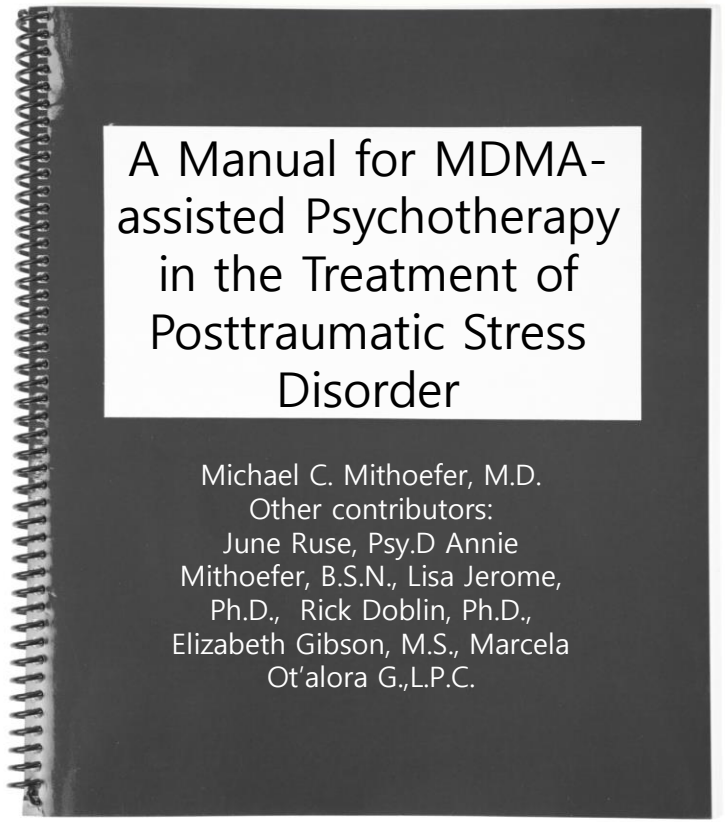
Boris D. Heifets & Robert C. Malenka
Stanford University School of Medicine
Cell, Vol. 166, Issue 2
July 14, 2016

Therapeutic Approach

Largely non-directive, supporting emerging experience.

Our adaptation of methods developed by Stanislav Grof and others

And Influenced by Richard Schwartz – Internal Family Systems Therapy



Magnifies Whatever is There

Affirming / Joyful

or

Difficult / Painful

MDMA from an IFS Perspective

Increase in Self Energy

- Often very pronounced
- Curiosity, clarity, compassion, confidence, creativity and connectedness

Increased awareness of parts

- And ability to un-blend

Video Clip from recent study with Veterans, Firefighters & Police Officers

A Catalyst

Brain changes

Affirming Experiences

Broader Scope

"The core of recovery is self awareness"

The Body Keeps the Score
Bessel van der Kolk

Often this means awareness of parts and Self

Marine Veteran

2 tours in Iraq as Humvee turret gunner

Middle of first MDMA session

75mg + 37.5mg

CAPS scores

Baseline ---------- 75

After 2 MDMA sessions ------ 6

1 year follow-up ---------- 19

Parts-work Scale based on IFS

Parts work/ IFS Occurrence Criteria for MDMA/PTSD studies

Michael Mithoefer, MD 10 October, 2011

Subject # _____ Session # _____ Rater: _____

1) Was the concept of parts brought up by the participant or the therapist?

Yes ____ No ____

If yes indicate which brought it up first: participant ____ therapist ____

If the answer to # 1 is "no" then all other questions are NA and should be skipped with the exception of question # 7 which should be answered in either case.

2) Did the therapist inquire further about the part or parts?

Yes ____ No ____

3) Did the therapist ask about the participant's feelings or attitude toward the part or parts?

Yes ____ No ____

Parts-work Scale based on IFS

4) Was there further exploration of the part or information elicited about the part, either spontaneously or prompted by the therapists' questions?

Yes _____ No _____

If yes indicate which: therapist's questions _____ , spontaneously _____ ,

both _____

5) Did the participant's attitude toward the part change in a positive direction?

Yes _____ No _____

6) Was there a sense that a part released old burdens, either explicitly or implicitly?

Yes _____ No _____

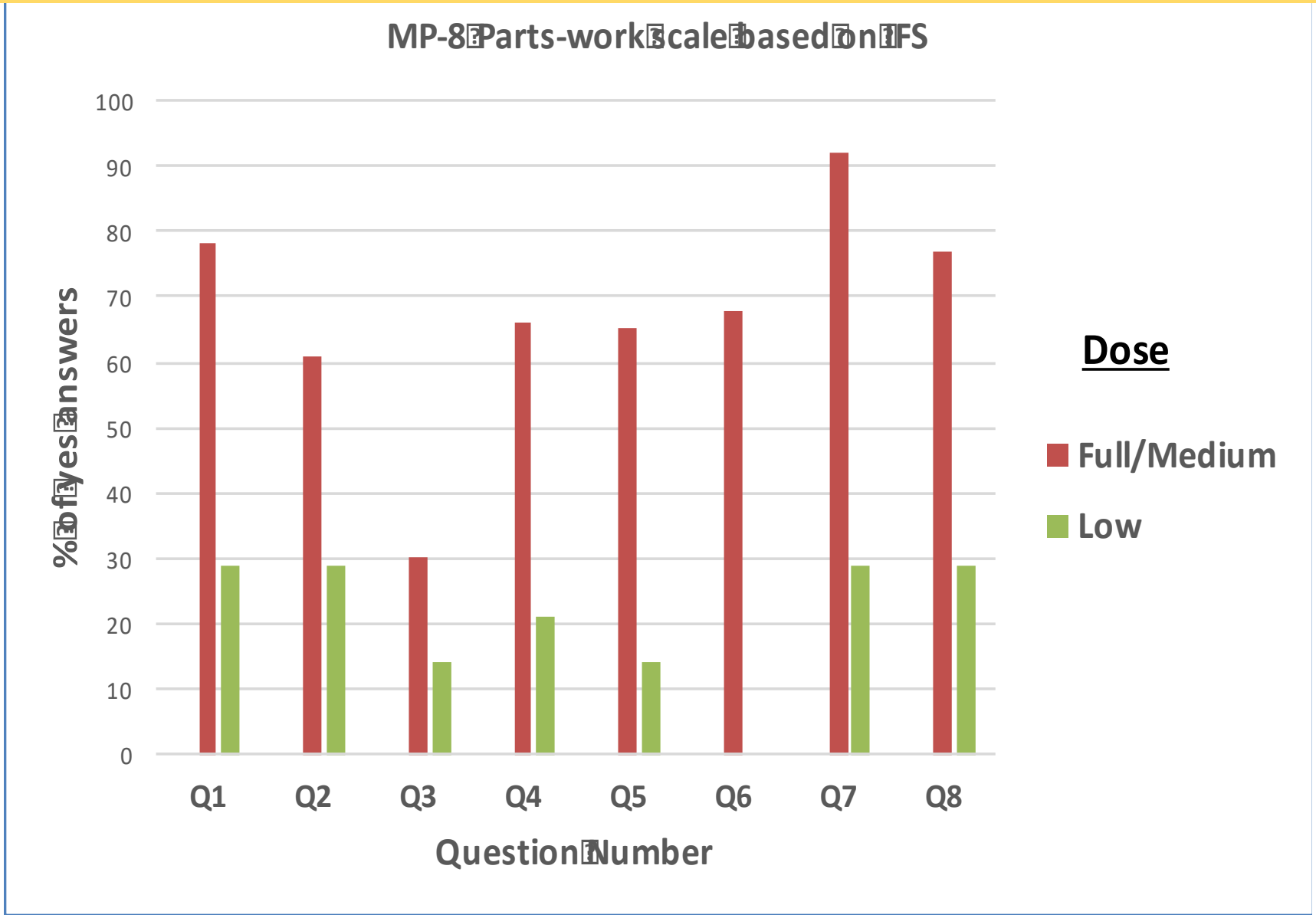
7) During the session was there an increase in qualities such as calmness, curiosity, clarity, compassion, confidence, creativity, courage, or connectedness.

Yes _____ No _____ (circle any of the qualities that apply)

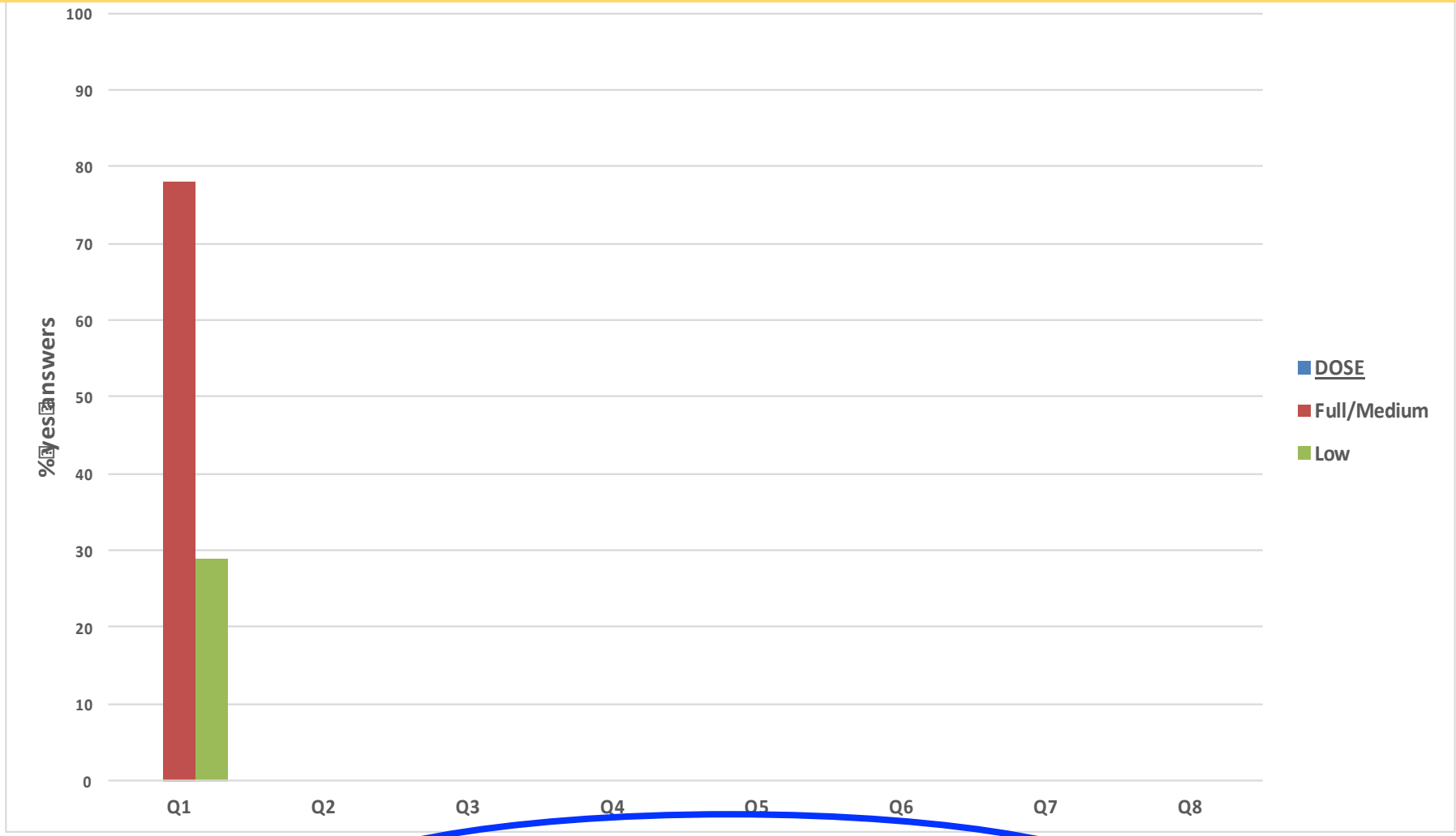
8) Did the symptoms or problems related to this part decrease over the course of therapy?

Yes _____ No _____

Parts-work Scale based on IFS

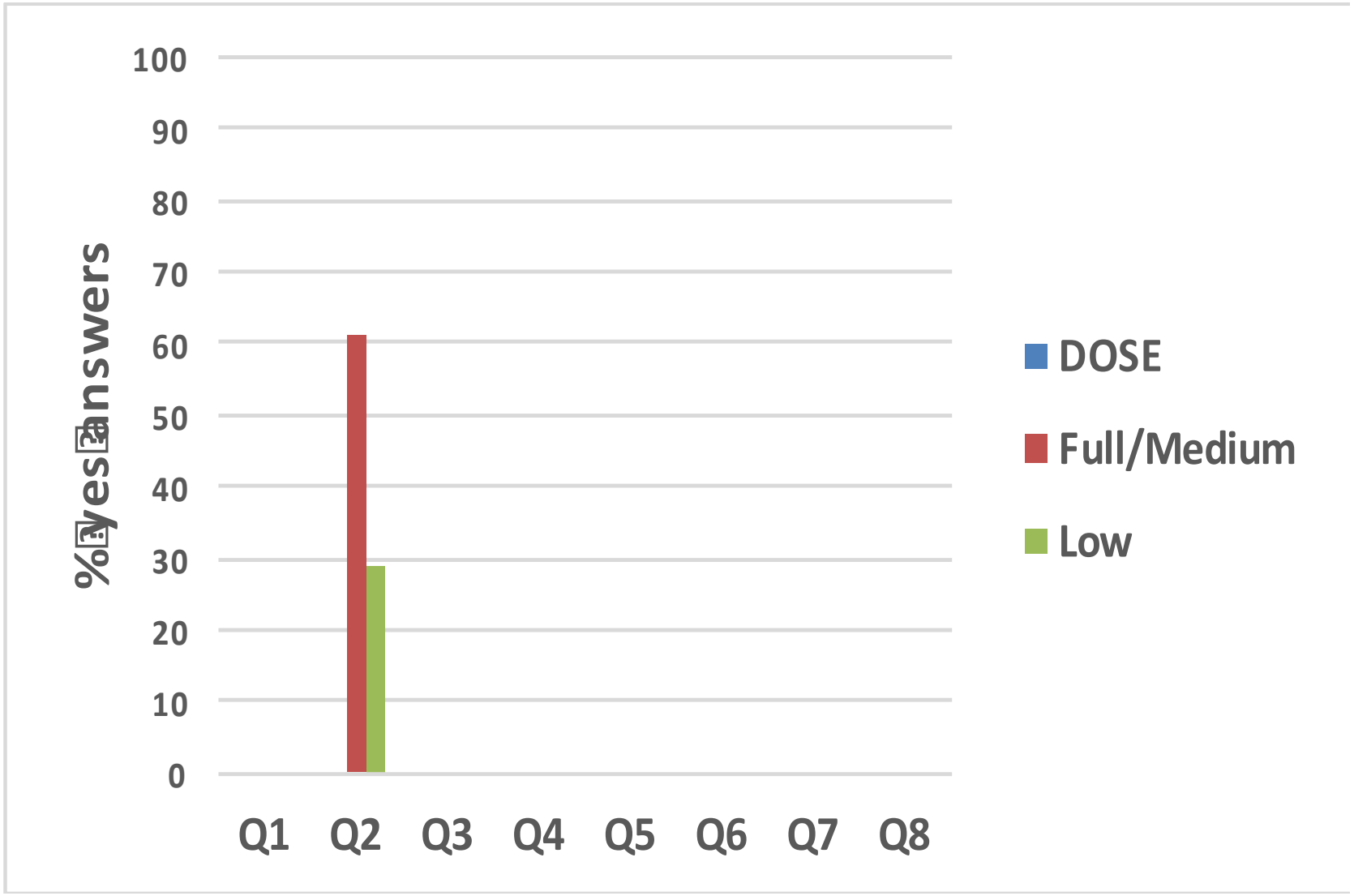


Question 1: Was the concept of parts brought up by the participant or therapists?

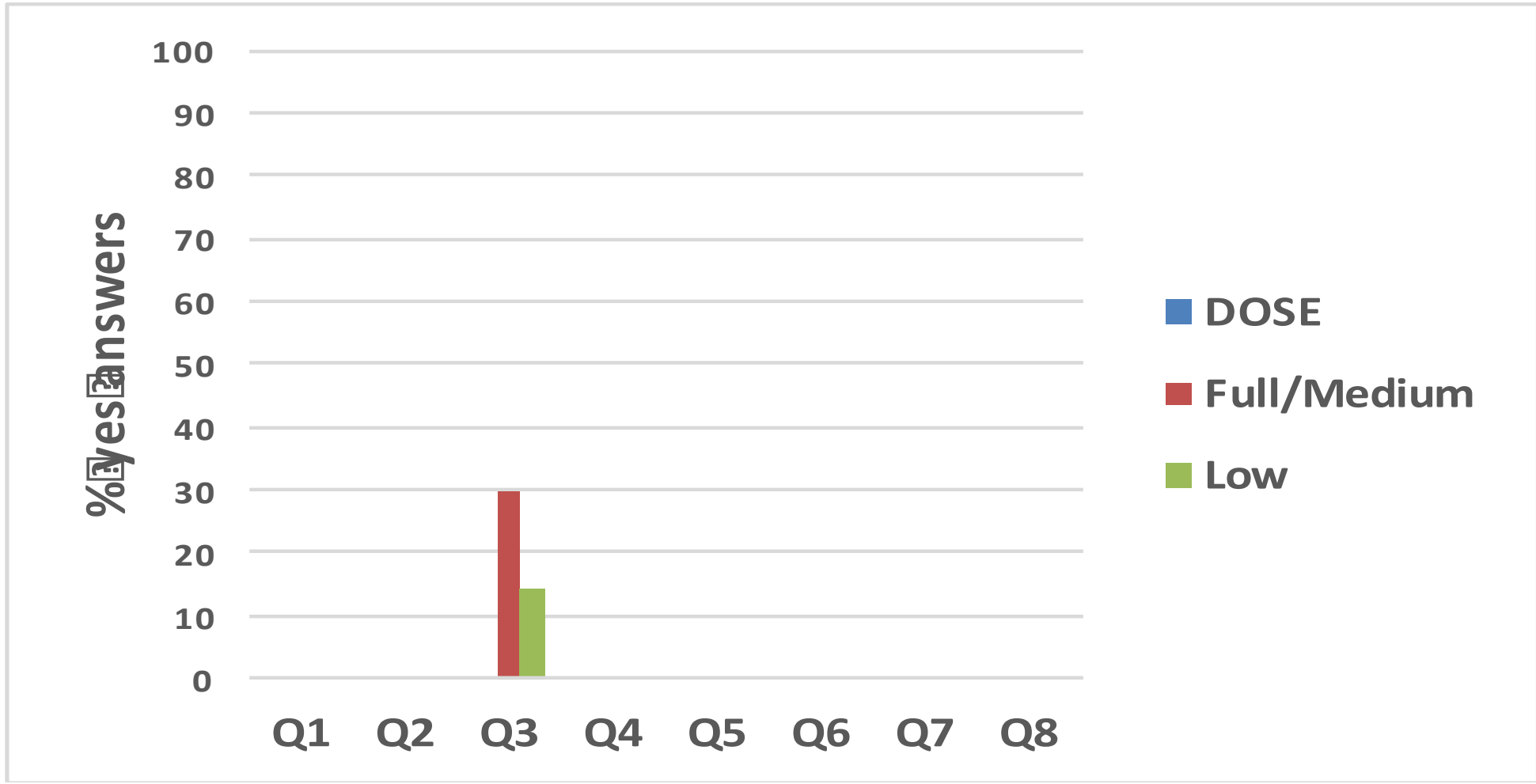


Brought up by participants 68 %

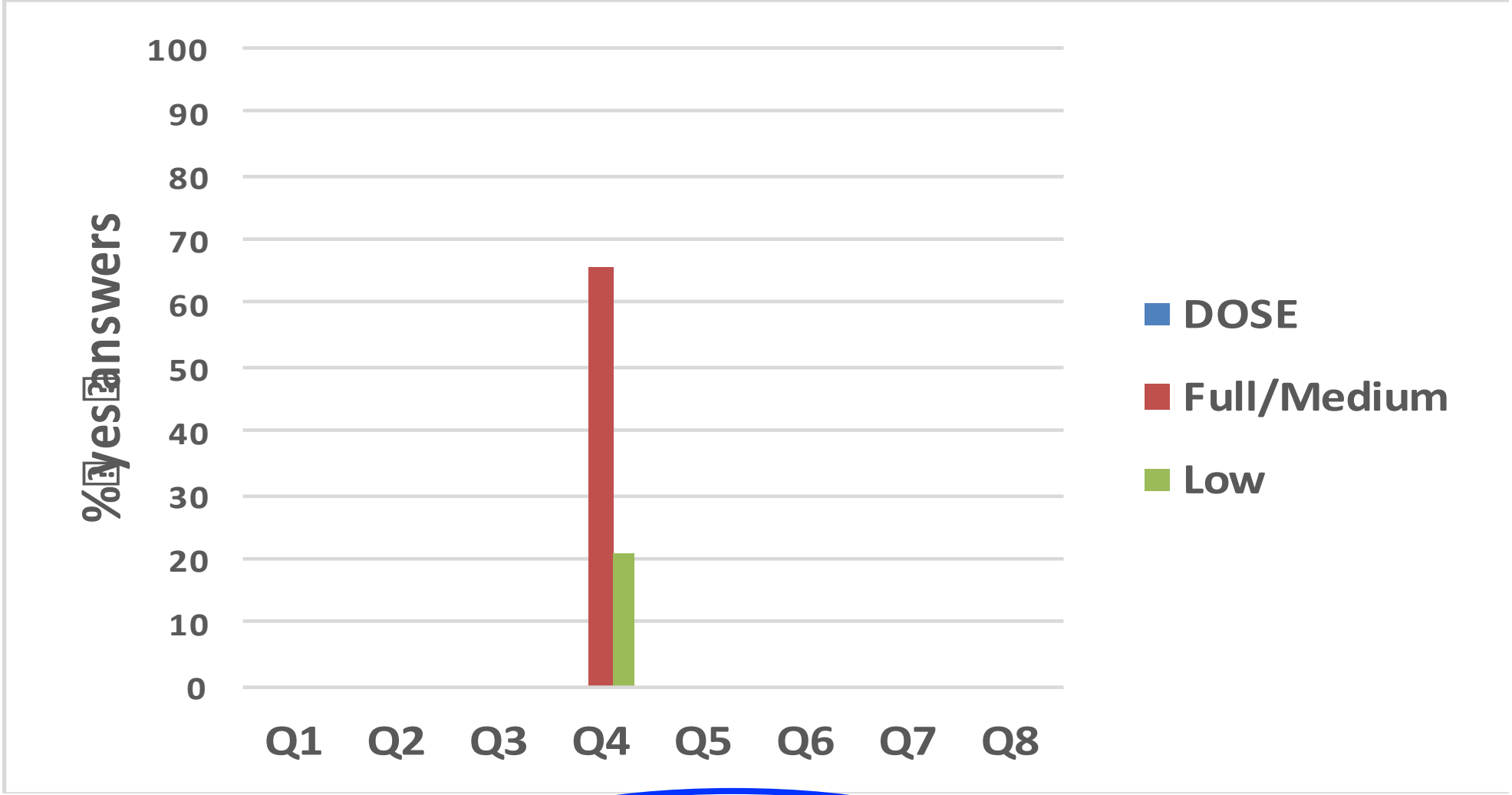
Question 2: Did the therapists inquire further about the part or parts?



Question 3: Did the therapists inquire further about the part of parts?

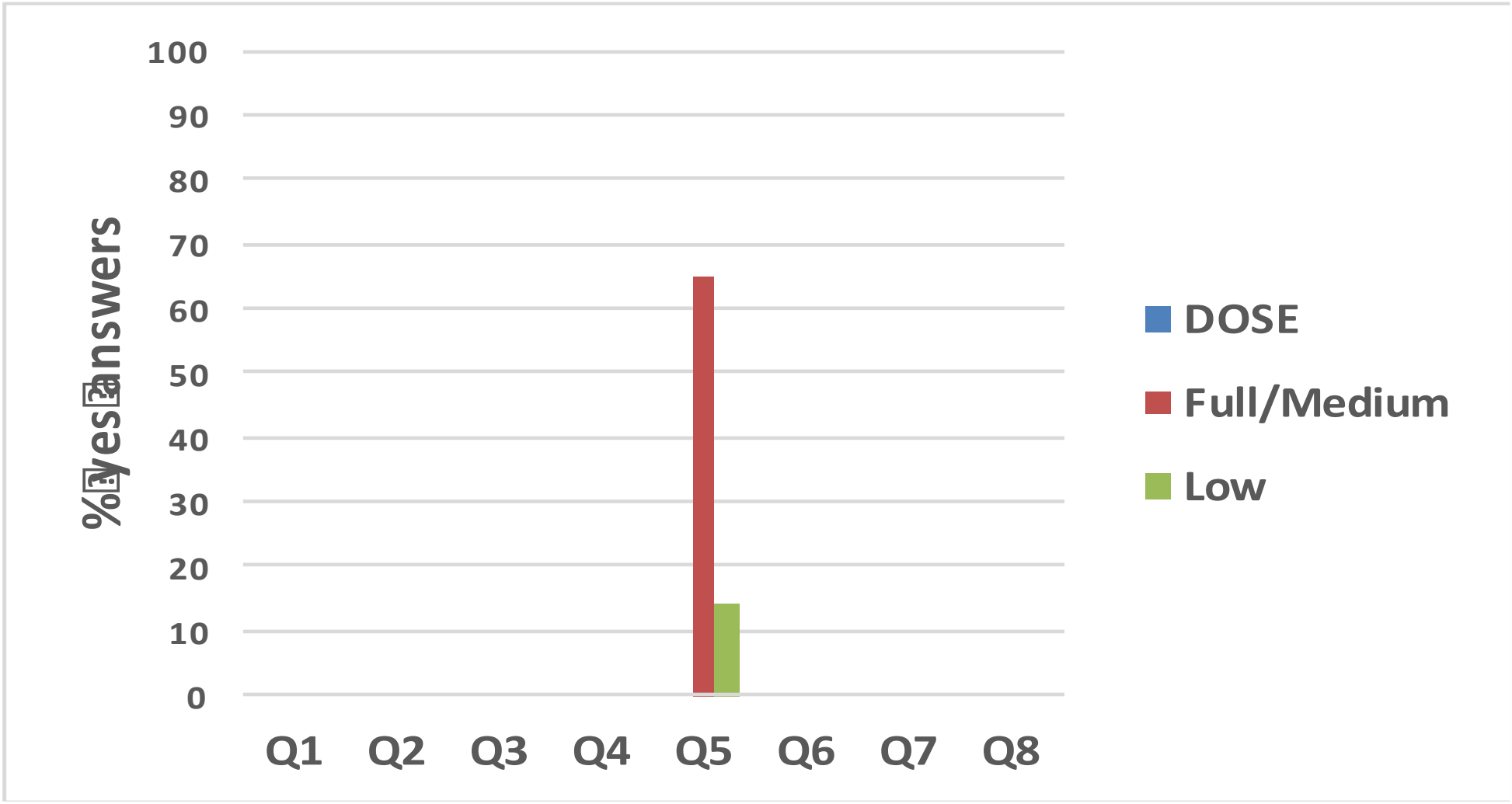


Question 4: Was there further exploration of the part or information elicited about the part?

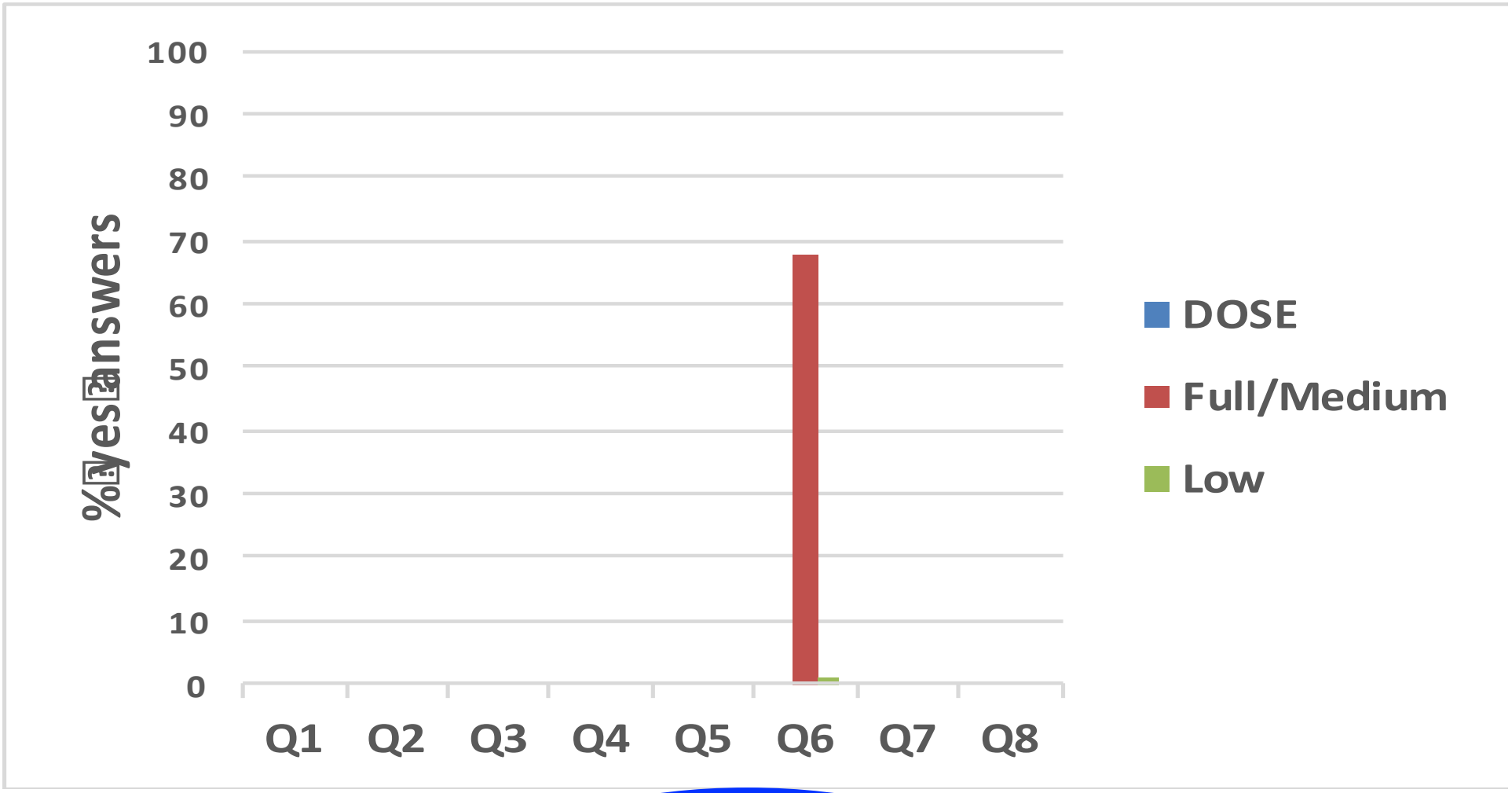


80% spontaneously

Question 5: Did the participant's attitude toward the part change in a positive direction?

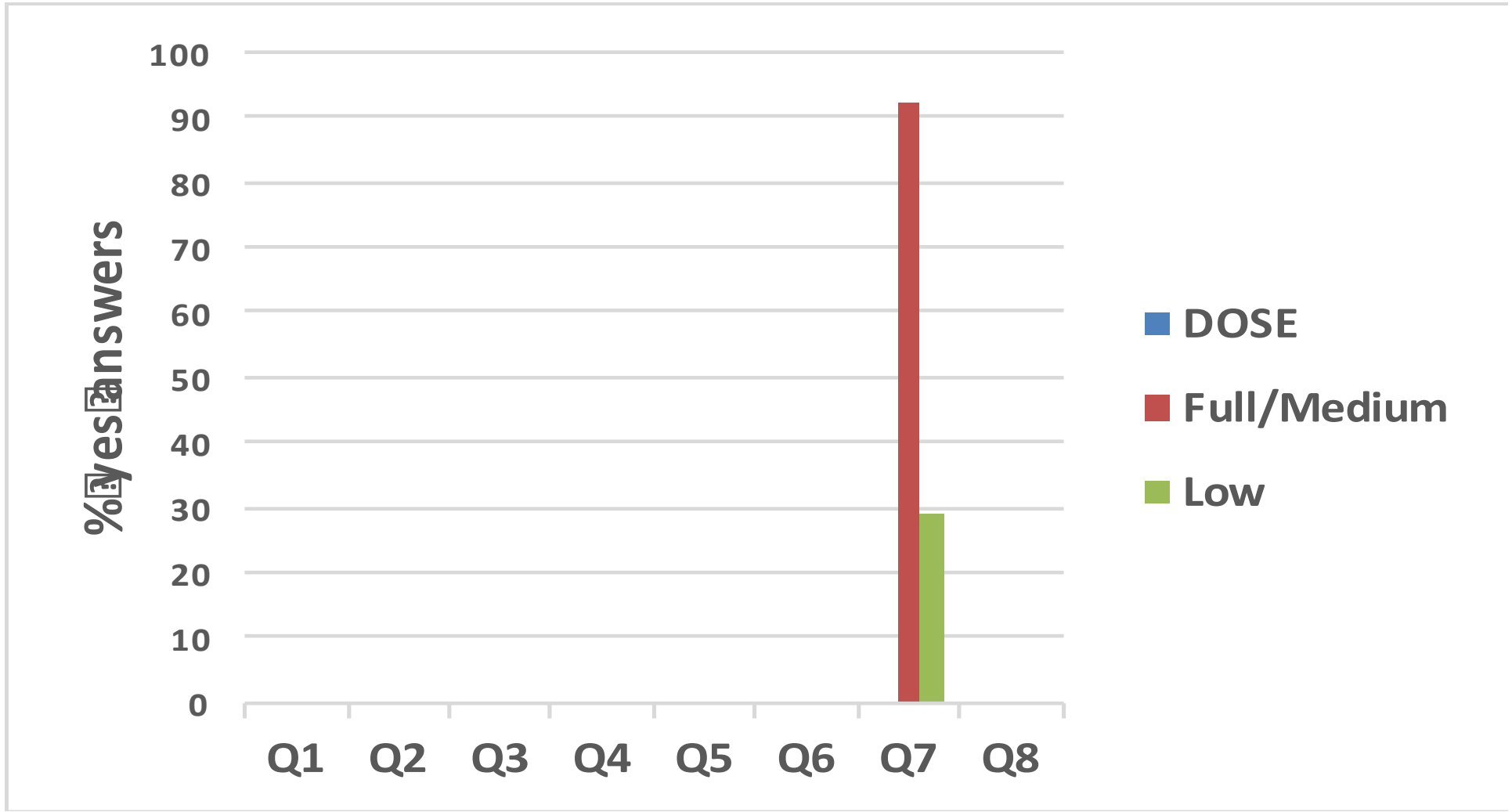


Question 6: Was there a sense that a part released old burdens, either explicitly or implicitly?

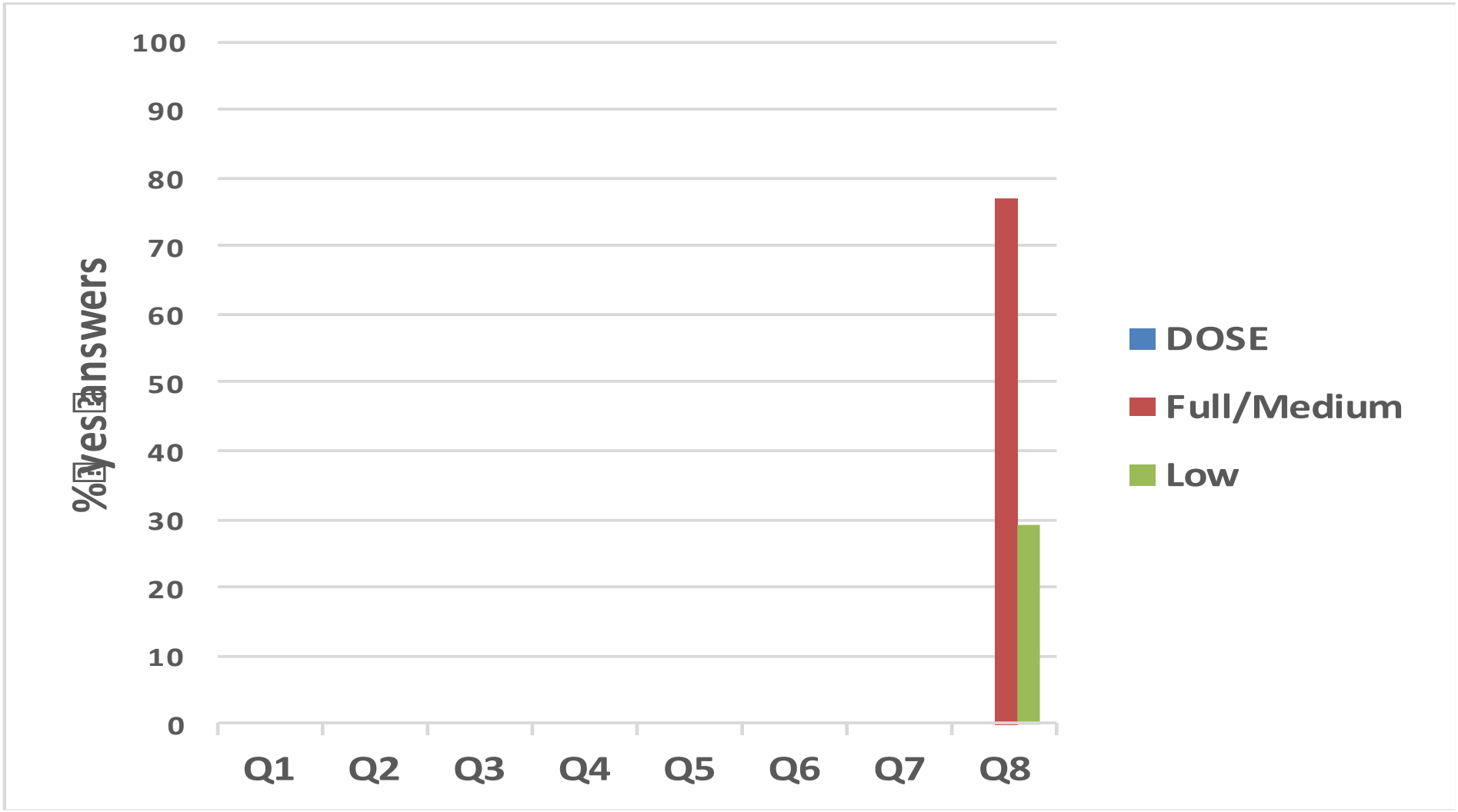


79% implicitly

Question 7: Was there an increase in qualities such as calmness, curiosity, clarity, compassion, confidence, creativity, courage, or connectedness?

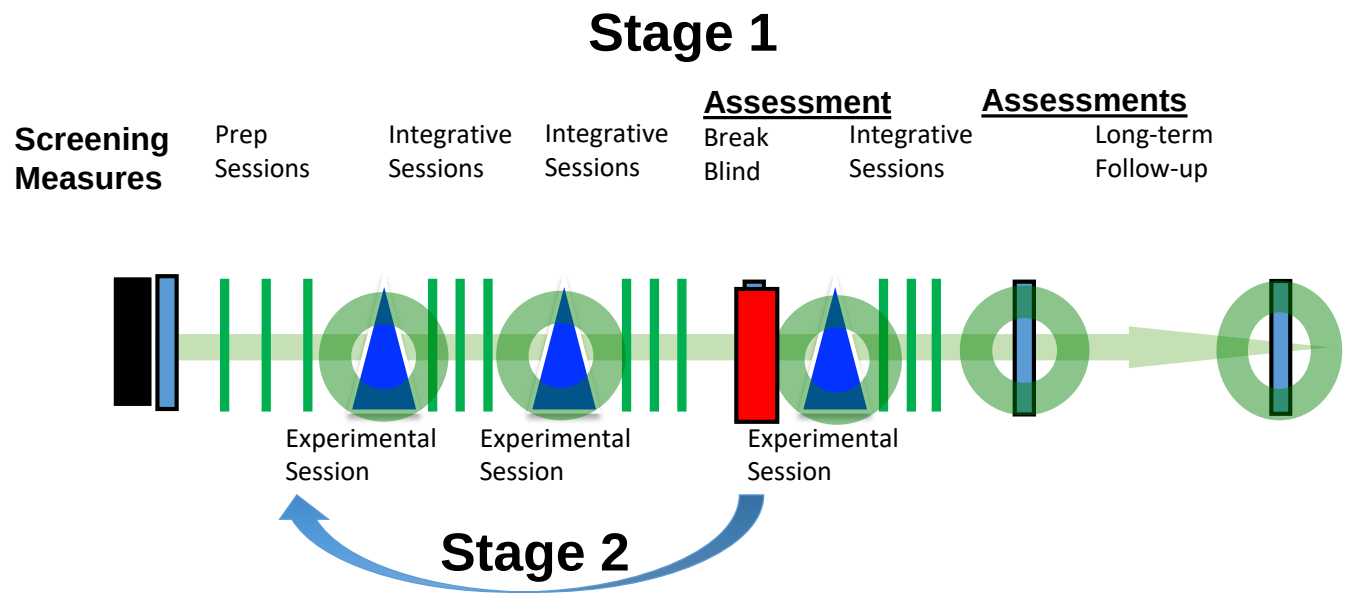


Question 8: Did the symptoms or problems related to this part decrease over the course of therapy?



MDMA-assisted Psychotherapy Study Design

Phase II: Chronic, Treatment-resistant PTSD



Open-label crossover for Low/Medium/Placebo Group

Phase 2 Clinical Trial (MP-1):

Original Paper

The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study

Psychopharm

Journal of Psychopharmacology
0(0) 1–14

DOI: 10.1177/0269881110378371
jop.sagepub.com
SAGE

Michael C Mithoefer[1], Mark T Wagner[2], Ann T Mithoefer[1], Lisa Jerome[3] and Rick Doblin[3]

Abstract

Case reports indicate that psychiatrists administered ±3,4-methylenedioxymethamphetamine (MDMA) as a catalyst to psychotherapy before recreational use of MDMA as 'Ecstasy' resulted in its criminalization in 1985. Over two decades later, this study is the first completed clinical trial evaluating MDMA as a therapeutic adjunct. Twenty patients with chronic posttraumatic stress disorder, refractory to both psychotherapy and psychopharmacology, were randomly assigned to psychotherapy with concomitant active drug ($n=12$) or inactive placebo ($n=8$) administered during two 8-h experimental psychotherapy sessions. Both groups received preparatory and follow-up non-drug psychotherapy. The primary outcome measure was the Clinician-Administered PTSD Scale, administered at baseline, 4 days after each experimental session, and 2 months after the second session. Neurocognitive testing, blood pressure, and temperature monitoring were performed. After 2-month follow-up, placebo subjects were offered the option to re-enroll in the experimental procedure with open-label MDMA. Decrease in Clinician-Administered PTSD Scale scores from baseline was significantly greater for the group that received MDMA than for the placebo group at all three time points after baseline. The rate of clinical response was 10/12 (83%) in the active treatment group versus 2/8 (25%) in the placebo group. There were no drug-related serious adverse events, adverse neurocognitive effects or clinically significant blood pressure increases. MDMA-assisted psychotherapy can be administered to posttraumatic stress disorder patients without evidence of harm, and it may be useful in patients refractory to other treatments.

Outcome Measures

Clinician Administered PTSD Scale (CAPS)

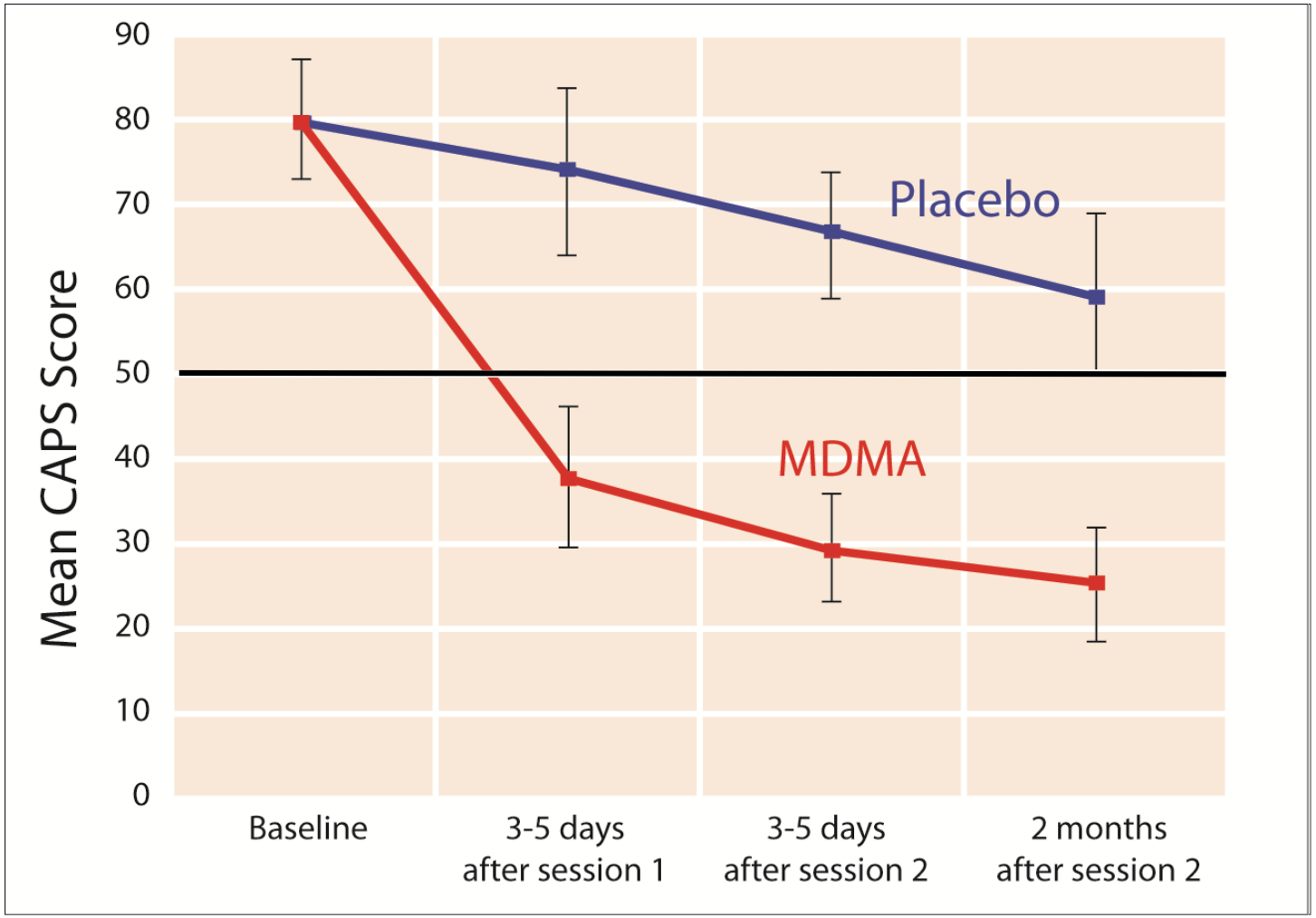
Impact of Event Scale Revised (IES-R)

Symptom Checklist 90-revised (SCL-90-R)

NEO Personality Inventory

Mithoefer MC et al. *J Psychopharm.* 2011;25(4):439-452

Mean CAPS Scores by Group



Time*Group Interaction *P*=0.015

Mithoefer MC et al. *J Psychopharm.* 2011;25(4):439-452

Stage 2

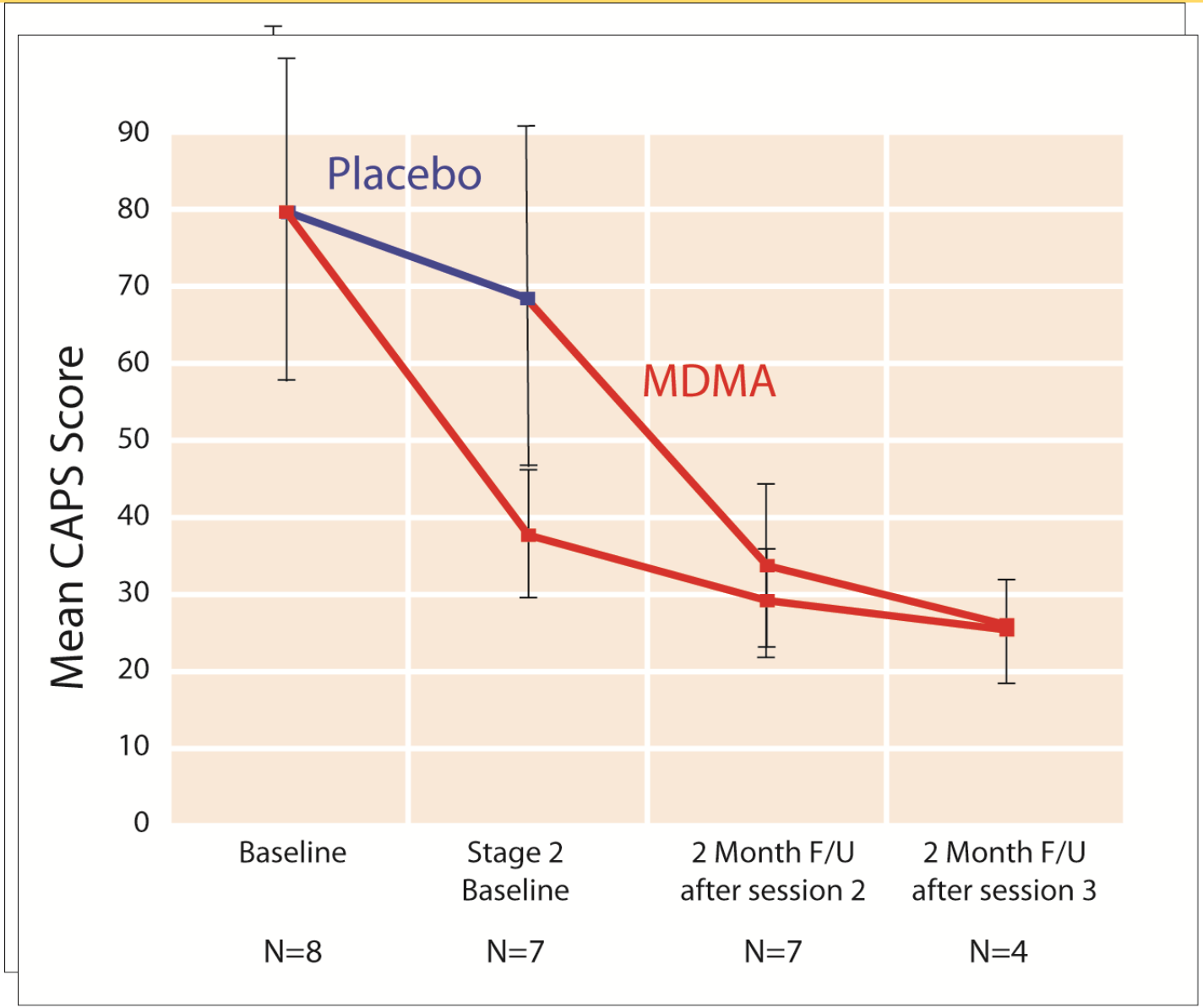
Open label MDMA-assisted therapy for participants who originally received placebo-assisted sessions

Integration non-drug therapy sessions as in Stage 1

7 of 8 placebo participants elected to participate

Mithoefer MC et al. *J Psychopharm.* 2011;25(4):439-452

Mean CAPS by Group - Stage 2 Crossover



Mithoefer MC et al. *J Psychopharm.* 2011;25(4):439-452

Neuropsychological Measures

Repeatable Battery for Assessment of Neuropsychological Status (RBANS)

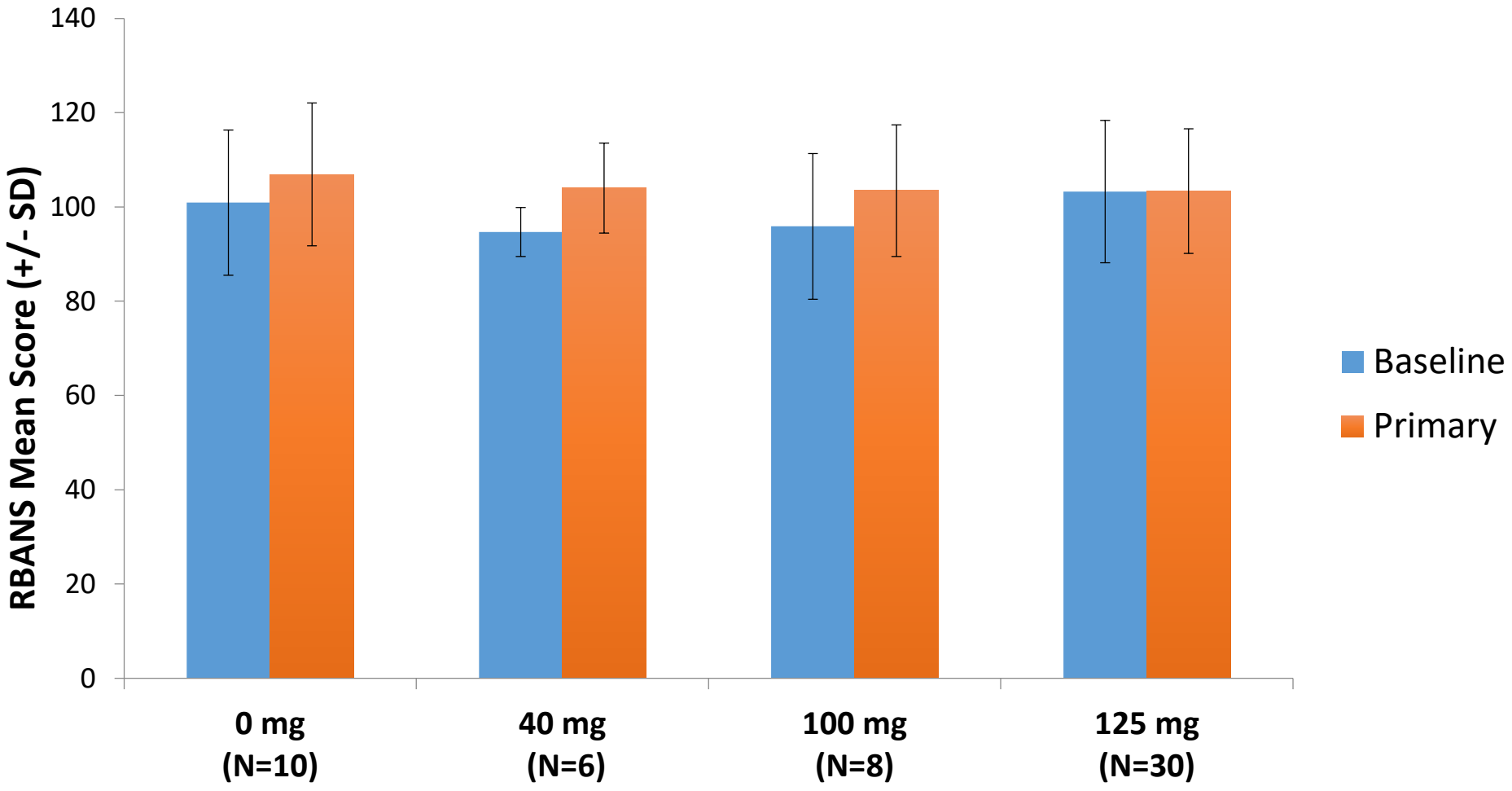
- Immediate memory, delayed memory, language, visuospatial/constructional, attention

Paced Auditory Serial Addition Task (PASAT)

Rey-Osterreith Complex Figure Test (RCFT)

Mithoefer MC et al. *J Psychopharm.* 2011;25(4):439-452

RBANS Baseline to 2-month follow-up



Data Cut-off: August 9, 2016

Long-term Follow-up

Original Paper

Durability of improvement in posttraumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study

Michael C Mithoefer[1,2], Mark T Wagner[3], Ann T Mithoefer[1,2], Lisa Jerome[4], Scott F Martin[5], Berra Yazar-Klosinski[6], Yvonne Michel[7], Timothy D Brewerton[1,8] and Rick Doblin[9]

Psychopharm

Journal of Psychopharmacology
0(0) 1–12

DOI: 10.1177/0269881112456611
jop.sagepub.com
SAGE

Long-term Follow-up

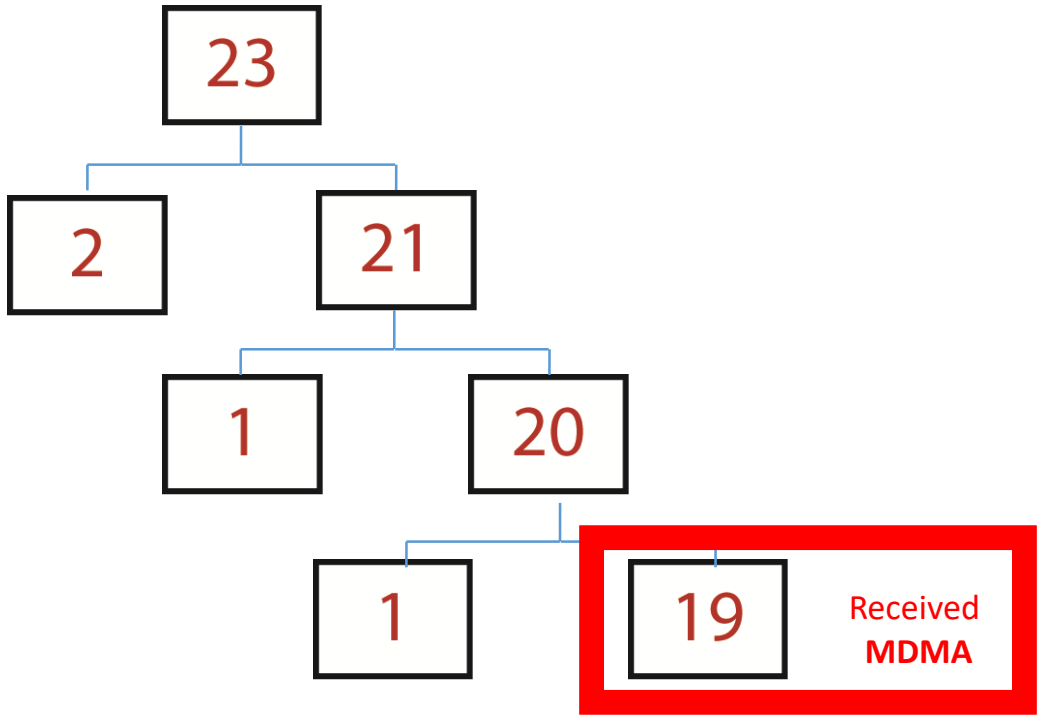
1 year or more after study completion

Repeat

- CAPS
- IES-R
- NEO
- Questionnaire

Mithoefer MC et al. *J Psychopharm.* 2013; 27(1):28-39

Participants in Data Analysis



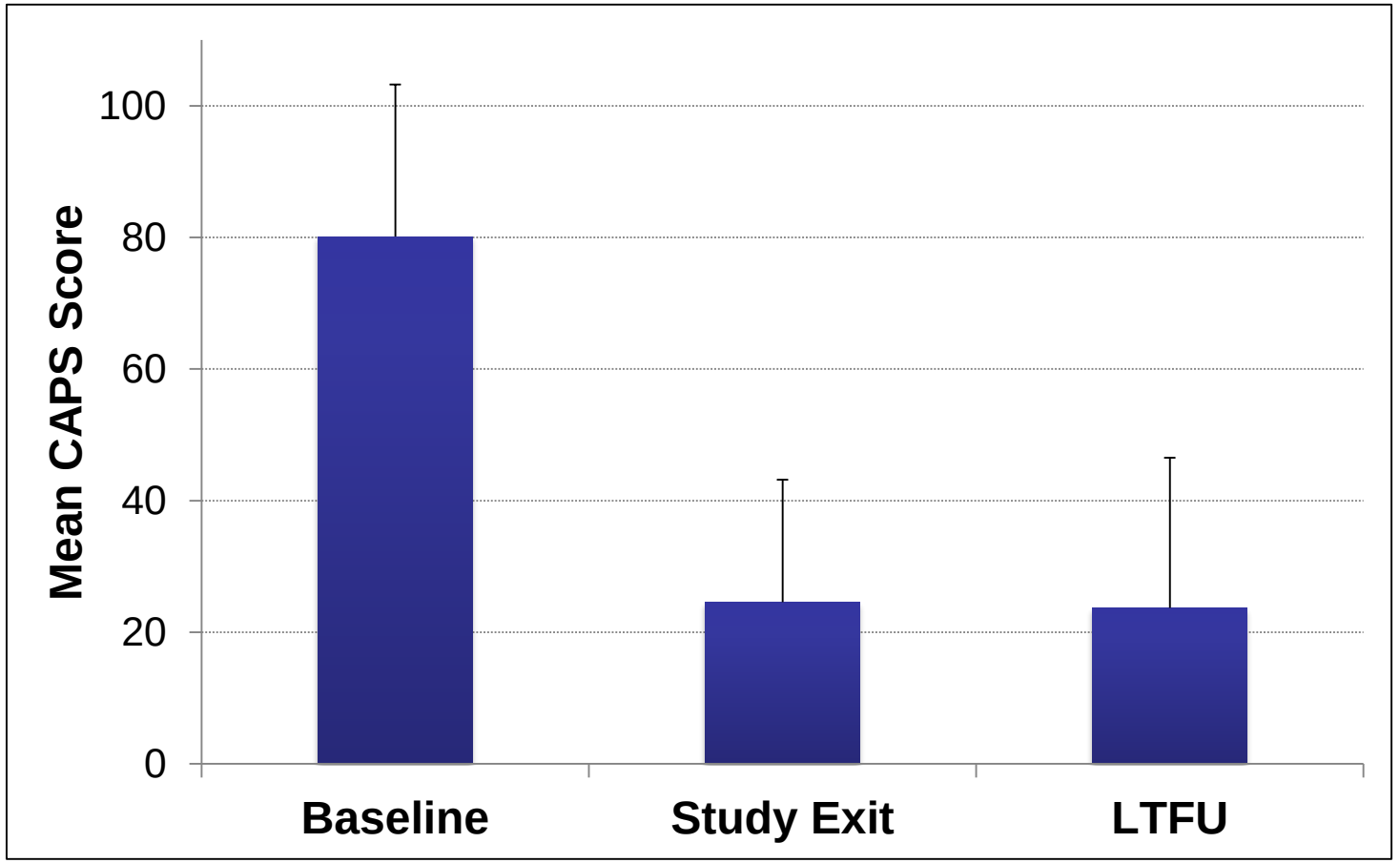
19 completed long-term follow-up questionnaire (LTFU)

16 completed LTFU and CAPS

Mithoefer MC et al. *J Psychopharm.* 2013; 27(1):28-39

Long-term Follow-up – Global MEAN CAPS

17 to 74 Months Post Final MDMA Session
(Mean = 45.4 Months, SD = 17.3)



* Error bars represent SD.

Mithoefer MC et al. *J Psychopharm.* 2013; 27(1):28-39

LTFU CAPS

Of 16 CAPS completers:

12% (2/16) relapsed

88% sustained benefit

Assuming 3 CAPS non-completers relapsed

26% relapsed (5/19)

74% sustained benefit

Mithoefer MC et al. *J Psychopharm.* 2013; 27(1):28-39

Recently Completed PTSD Study

A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction With Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers With Chronic PTSD

Michael C. Mithoefer, MD, Annie T. Mithoefer, BSN,
Mark T. Wagner, PhD, Joy Wymer, PhD

Charleston, SC

NCT01211405

Outcome Measures

Clinician Administered PTSD Scale (CAPS)

Beck Depression Inventory (BDI-II)

Global Assessment of Functioning (GAF)

Posttraumatic Growth Inventory (PTGI)

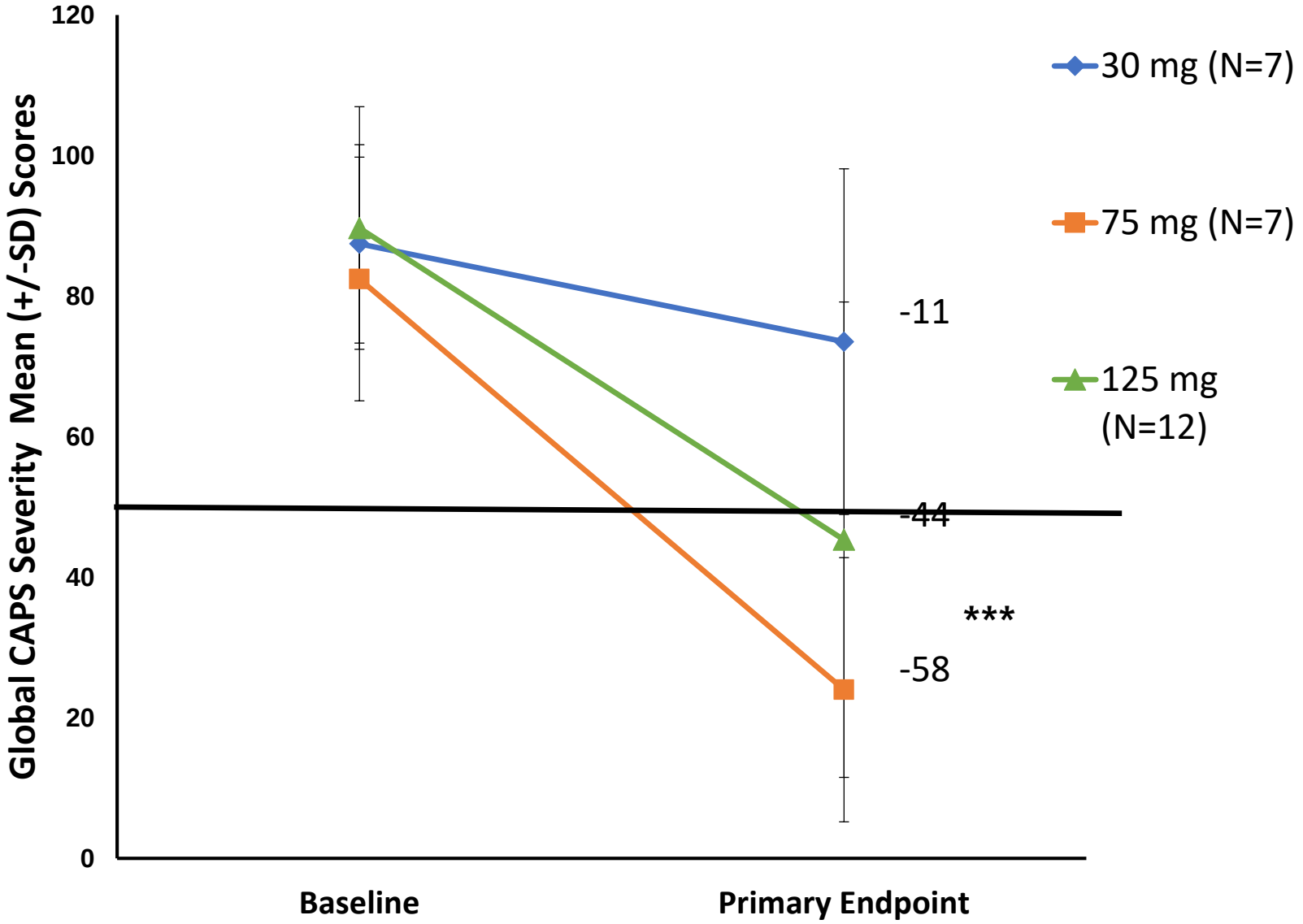
Pittsburg Sleep Quality Index (PSQI)

States of Consciousness Questionnaire (SOCQ)

NEO Personality Inventory (NEO)

PTSD Symptoms (CAPS) Baseline and after 2 sessions

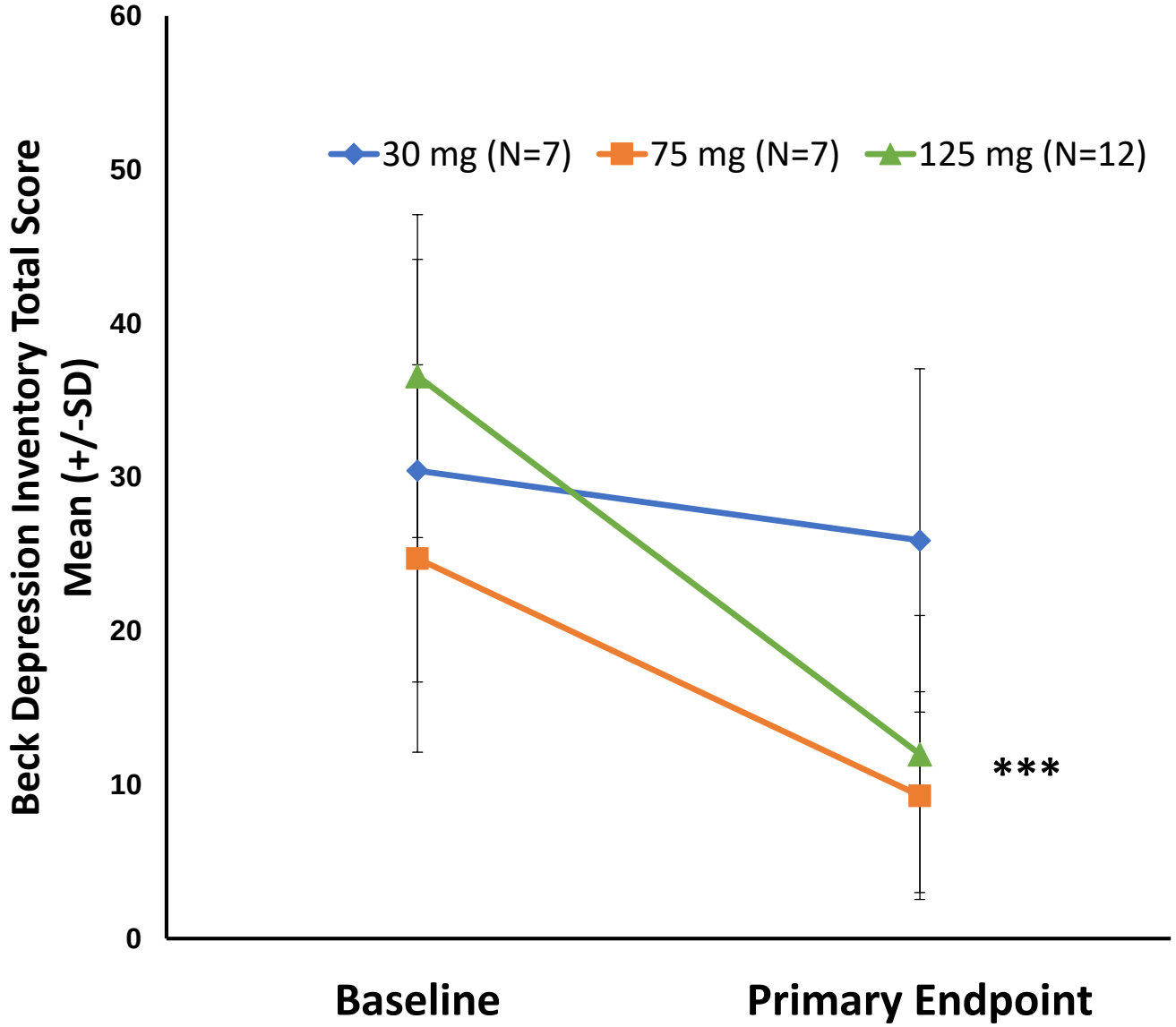
(Preliminary)



***p<0.001 (75 mg and 125 mg vs. 30 mg), ANOVA of Difference Scores (Primary – Baseline)

Depression Symptoms - BDI-2

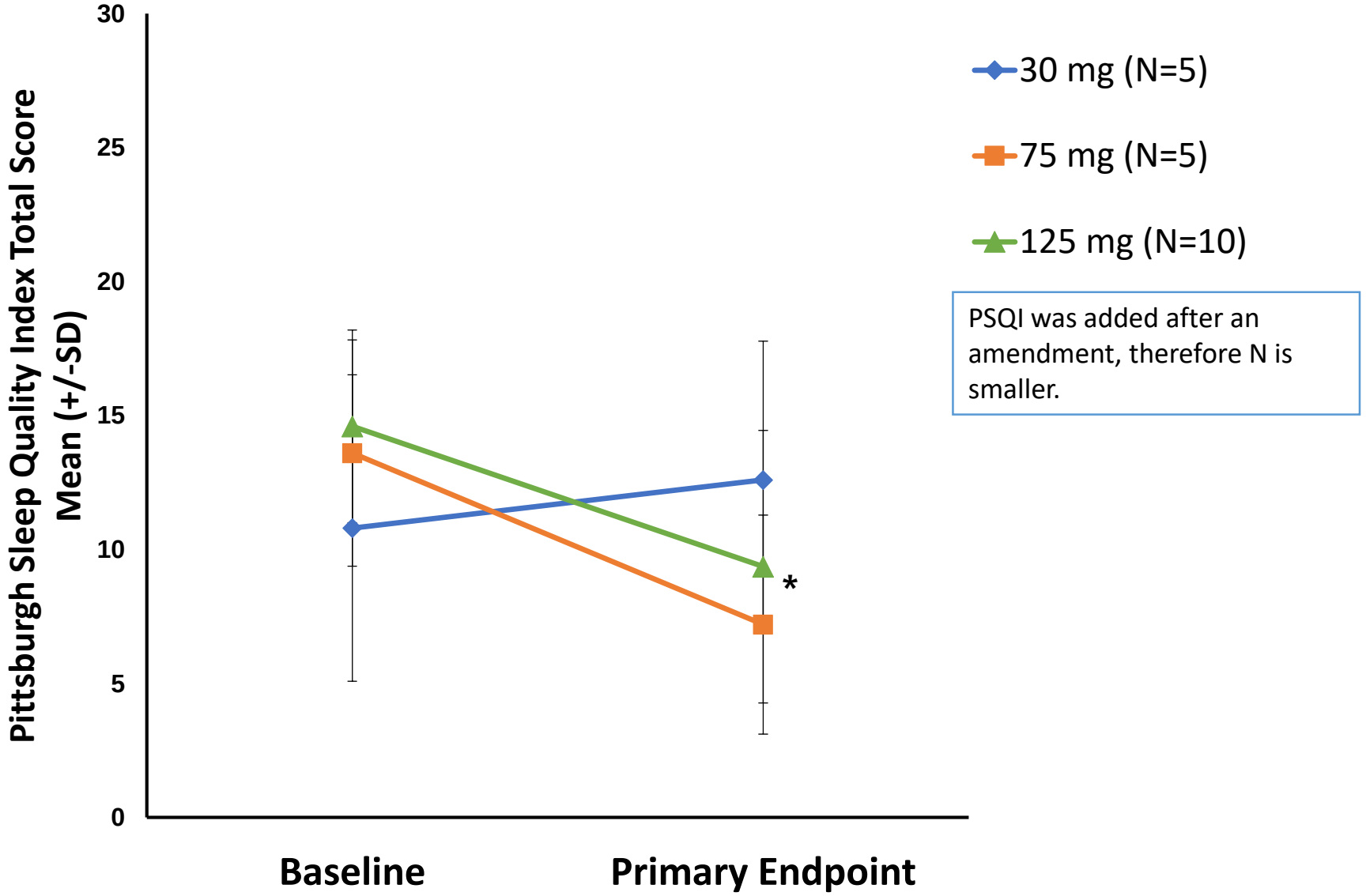
(Preliminary)



***p<0.001 (125 mg vs. 30 mg), ANOVA of Difference Scores (Primary – Baseline)

Pittsburg Sleep Quality Index

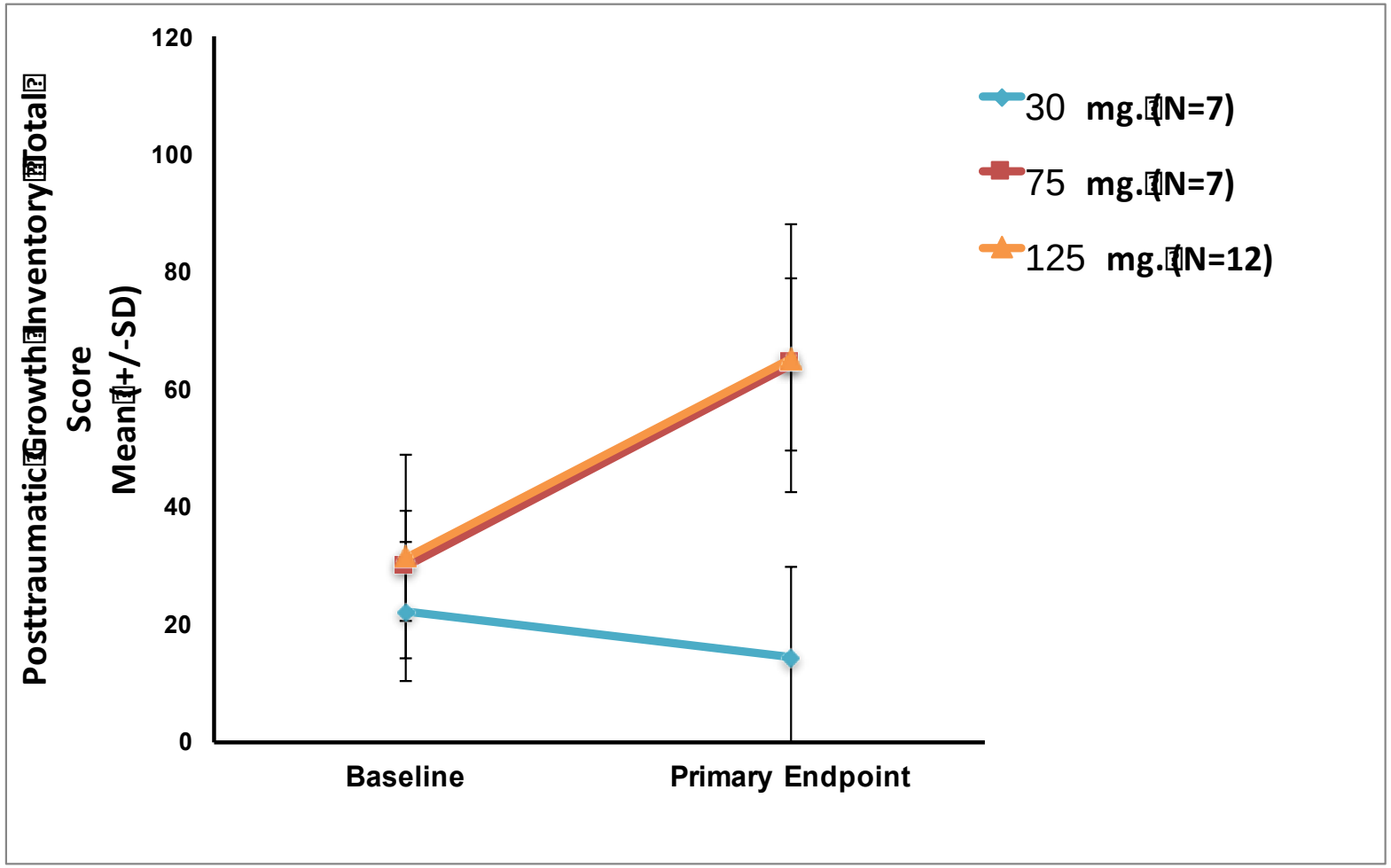
(Preliminary)



*p<0.05 (75 and 125 mg vs. 30 mg), ANOVA of Difference Scores (Primary – Baseline)

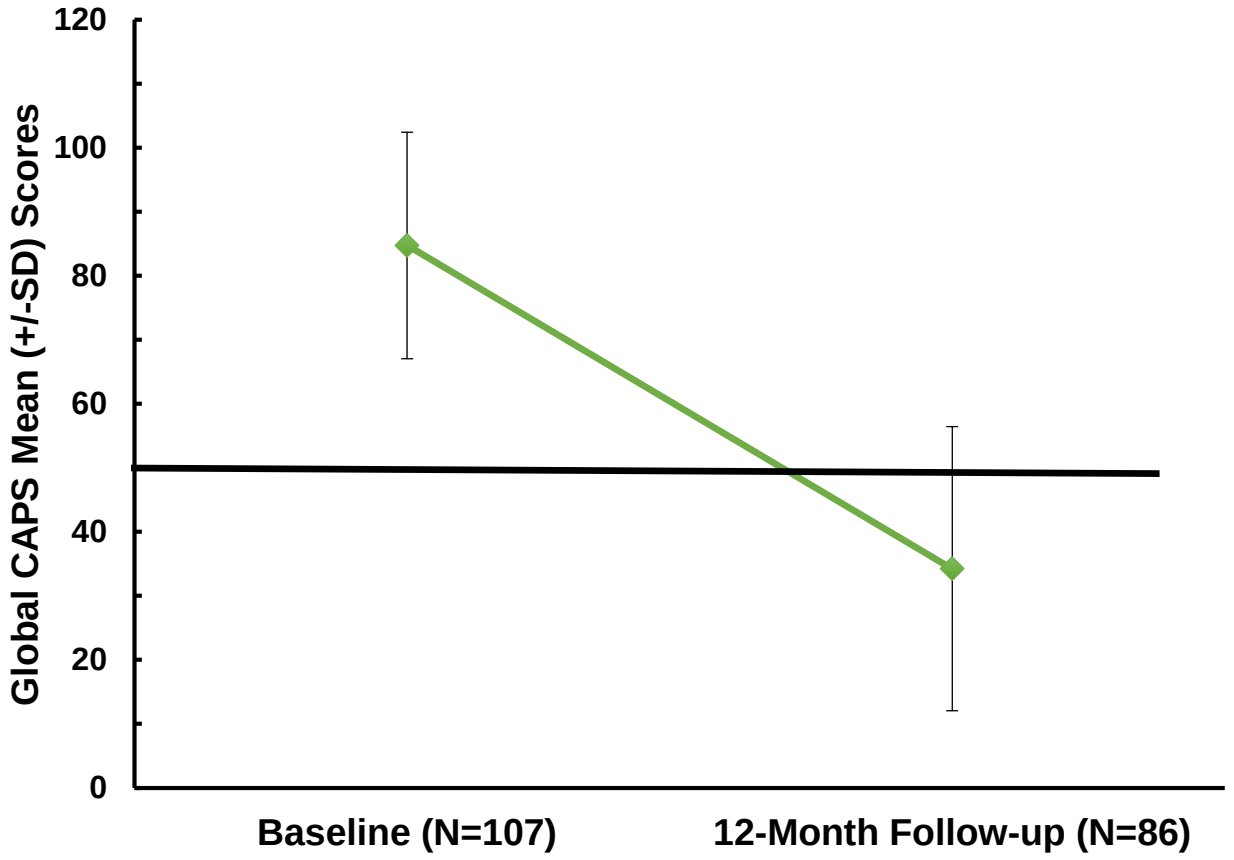
Posttraumatic Growth Inventory

(Preliminary)



NCT01211405

Preliminary outcomes
All MAPS MDMA-assisted psychotherapy PTSD Studies

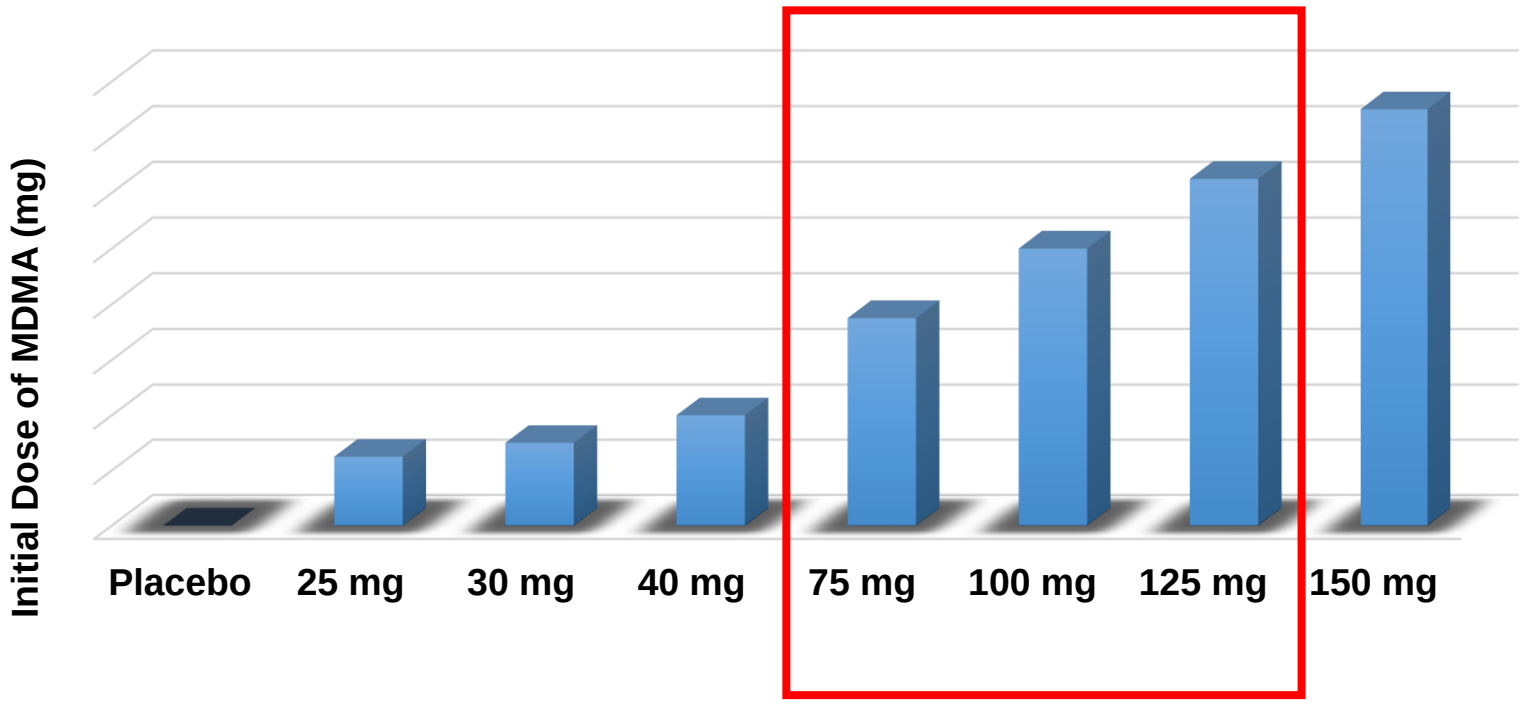


Preliminary Cumulative Effect Size

MDMA-Assisted Psychotherapy for PTSD – 6 Studies

Study	Sample	Dose Comparison	Effect Size	Effect
Published **Charleston (MP-1)**	Intent to Treat N=23	125 mg vs. 0 mg	1.6	Large
Published **Switzerland (MP-2)**	Intent to Treat N=14	125 mg vs. 25 mg	1.6*	Large
Vancouver (MP-4)	Intent to Treat N=6	125 mg vs. 0 mg	-1.3	-
Charleston (MP-8)	Intent to Treat N=26	Active (75-125 mg) vs. 30 mg	1.4	Large
Israel (MP-9)	Intent to Treat N=8	125 mg vs. 25 mg	1.3	Large
Boulder (MP-12)	Intent to Treat N=26	Active (100-125 mg) vs. 40 mg	0.4	Small
All Studies	**Intent to Treat N=105**	**Active (75-125 mg) vs. Comparator (0-40 mg)**	**0.9**	**Large**

Range of doses explored in MAPS Phase 2 MDMA Studies



Six most common Reactions – day of Experimental Sessions

	0-40 mg N=31		**75-125 mg** N=74		Open Label N=78	
	N	%	N	%	N	%
Anxiety						
Any	17	54.8%	52	70.3%	39	50.0%
Severe	5	16.1%	5	6.8%	8	10.3%
Fatigue						
Any	18	58.1%	36	48.6%	33	42.3%
Severe	0	0.0%	2	2.7%	0	0.0%
Headache						
Any	22	71.0%	38	51.4%	35	44.9%
Severe	0	0.0%	0	0.0%	2	2.6%
Jaw Clenching, Tight Jaw						
Any	6	19.4%	46	62.2%	47	60.3%
Severe	0	0.0%	4	5.4%	3	3.8%
Lack of Appetite						
Any	7	22.6%	35	47.3%	38	48.7%
Severe	1	3.2%	1	1.4%	1	1.3%
Nausea						
Any	7	22.6%	29	39.2%	29	37.2%
Severe	0	0.0%	4	5.4%	2	2.6%

Vital Signs

(N=152 MDMA sessions – from 2 clinical trials)

	Inactive Placebo (N=8)	Active Placebo (low dose MDMA) (N=7)	75 mg. (with optional supplemental half dose) (N=7)	125 mg. (with optional supplemental half dose) (N=27)
	Max	Max	Max	MAX
Systolic BP	157	155	179	194
Diastolic BP	102	99	118	113
Heart Rate (BPM)	107	102	123	152
Temperature (C)	37.55	37.9	37.8	38.5
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Systolic BP	111.5 (12.8)	132.3 (14.0)	147.0 (14.4)	143.7 (16.4)
Diastolic BP	72.4 (9.7)	85.5 (7.5)	91.4 (12.1)	87.7 (8.1)
Heart Rate (BPM)	70.1 (10.2)	81.1 (15.9)	96.2 (16.1)	97.5 (18.1)
Temperature (C)	36.5 (0.5)	37.0 (0.4)	37.1 (0.5)	37.0 (0.6)

Percentage of Subjects Reporting Serious Adverse Events Post-Drug During Treatment Period: Whether Related or Not to MDMA

Dose	Comparator Dose (25-40 mg)	Active Dose (75-125 mg)	Open Label (100-150 mg)
Subjects Per Dose Group	N=21 N (%)	N=74 N (%)	N=78 N (%)
Cardiovascular			
Ventricular Extrasystoles (exacerbation)	--	--	1 (1.3%)
Injuries			
Clavicle Fracture (auto accident)	--	1 (1.3%)	--
Lower Limb Fracture	--	1 (1.3%)	--
Nervous System			
Syncope	--	1 (1.3%)	--
Psychiatric			
Suicidal Ideation	1 (4.8%)	--	--

Onward to Phase 3

Photo by Nirvan Mullick, PrescriptionX – The Rick Doblin Story

Video of a female veteran in MDMA/PTSD study

This participant has given permission to show her video
only with her face obscured,
and only to workshop participants.

Video streaming must be turned off

Deep appreciation for the MAPS team, members, donors, investigators
And especially
All the study participants!

Clinical Research Team

Amy Emerson, Director of Clinical Research
Berra Yazar-Klosinski, PhD, Clinical Research Scientist
Rebecca Matthews, Clinical Trial Leader
Charlotte Harrison, Senior Clinical Research Associate
Alia Lilienstein, MD, Clinical Research Associate-Physician

Allison Feduccia, PhD, Clinical Data Scientist
Colin Hennigan, Clinical Data Manager
Allison Wilens, Clinical Study Associate
Ilsa Jerome, PhD, Research & Information Specialist

Clinical Investigators

Michael Mithoefer, MD, Lead Clinical Investigator, Medical Monitor
Annie Mithoefer, BSN, Co-Investigator, Charleston
Marcela Ot'alora, MA, LPC, Primary Investigator, Boulder
Bruce Poulter, Co-Investigator, Boulder
Moshe Kotler, MD, Primary Investigator, Israel
Peter Oehen, MD, Primary Investigator, Switzerland
Ingrid Pacey, MD, Primary Investigator, Canada

Principal investigator:
Michael Mithoefer, MD
208 Scott Street, Mount Pleasant, SC 29464
mmithoefer@mac.com

Co-investigators:
Annie Mithoefer BSN, Mark Wagner, PhD, Joy Wymer, PhD

Acknowledgments:
Sarah Sadler, Sarah Brazwell, Berra Yazar-Klosinski, PhD, Ben Shechet,
Rebecca Mathews, Alli Feduccia, PhD, Ilsa Jerome, PhD
Amy Emerson, Rick Doblin, PhD

Sponsor:
Multidisciplinary Association for Psychedelic Studies (MAPS)
www.maps.org

References:

1. Mithoefer, M. et al. J Psychopharmacol, 2011 and 2013.
2. Feduccia, A. et al. J Eur Neuropsychopharmacology 2010.
3. Gamma, A. et al. Neuropsychopharmacology 2000.
4. Dumont, G et al. J Social Neuroscience, 2009.
5. Heifets, B and Malenka, R. Cell, 2016.