

Case Study: Healing Emotion After Loss (HEAL) Trial

Complicated grief (CG) is a form of acute grief in which something interferes with adaptation to loss. Also referred to as Prolonged Grief Disorder (PGD).



Estimated population prevalence: 7% of bereaved people

Rate is much higher (about 40%) among those bereaved by violent death

Center for Prolonged Grief



[WORKSHOP: February 11 \(9am – 5pm EST\): The Big Picture: PGDT Principles and Procedures. Online. 6.5 CE hours. Register now.](#)



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The Center Offers Consultation Treatments to PGD Patients (especially during COVID-19)

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Our research has produced clinical assessment and treatment tools that can be used with confidence.

We began prolonged grief (previously known as complicated grief) treatment research in the 1990s when colleagues at the University of Pittsburgh found that grief symptoms did not respond to treatments for depression.

In 2000, we published a pilot study of a new Complicated Grief Therapy (CGT), now known as Prolonged Grief Disorder Therapy (PGDT) and received NIMH funding to test CGT (PGDT). Results published 2005 showed that CGT (PGDT) was nearly twice as effective as Interpersonal Psychotherapy (IPT), a very good treatment for depression.

In 2008 we received an NIMH grant to study CGT (PGDT) in older adults. Results published in 2014 again showed that CGT (PGDT) was twice as effective as IPT for complicated grief.

A third NIMH-funded study tested the efficacy of antidepressant medication at 4 different clinical research sites. Results published in 2016 again showed CGT (PGDT) to be very effective while we did not show efficacy of antidepressant medication. However, when we used an antidepressant with CGT (PGDT), symptoms of depression improved compared to using a placebo.

Complicated grief (CG) is a form of acute grief in which something interferes with adaptation to loss



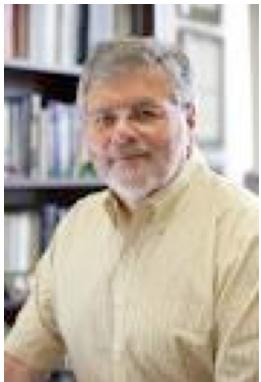
Healing Emotion After Loss (HEAL) is a large, multi-site, randomized controlled trial (RCT) to optimize treatment of CG with Columbia University as the leading site and data coordinating center

THE STUDY PI'S

Optimizing treatment for complicated grief (HEAL STUDY)



Naomi Simon MD
PI MGH site



Sid Zisook MD
PI San Diego site



Kathy Shear MD and Naihua Duan PhD
PI's Coordinating Site
Columbia University



Chip Reynolds MD
PI Pittsburgh site

Study coordinators, statisticians, consultant, CGT supervisors and therapists, assessment raters, etc...



BACKGROUND

The majority of treatment seeking patients with CG have received antidepressant medication

There are mixed results of open label studies of antidepressants for CG

OPEN TRIALS OF ESCITALOPRAM

	n	CG symptom reduction (ICG)
Hensley et al (2009)	14	21%
Simon et al (2007)	4	76%
Shear et al (2006)	17	24%

EARLY OPEN MEDICATION TRIALS

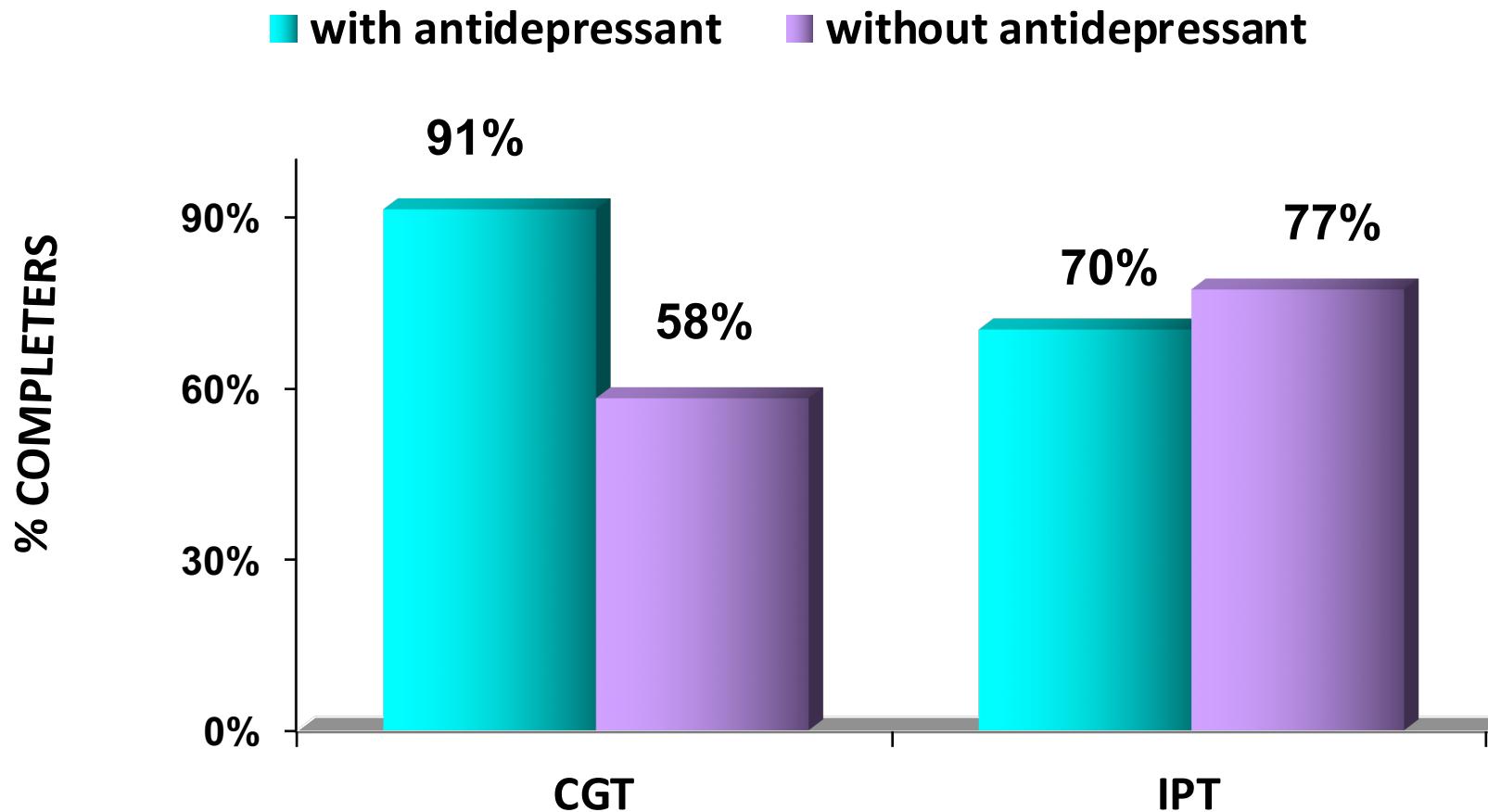
	n	CG symptom reduction
Zygmont et al (1998)	15 (Paroxetine with pilot CGT)	48%
Pasternak et al (1991)	13 (NTP for bereavement MDD)	9%

Antidepressant medication was associated with lower drop out rate from Complicated Grief Therapy (CGT)



Simon et al, Psychiatry Research, 2008: Simon et al, AJP, 2007

SECONDARY ANALYSIS



CGT=Complicated Grief Therapy

IPT= Interpersonal Therapy, for loss

NEXT STEP: HEAL

A LARGE NIMH-FUNDED RANDOMIZED
CONTROLLED STUDY OF
ANTIDEPRESSANT EFFICACY

STUDY SITES: Columbia (Coordinating Center)

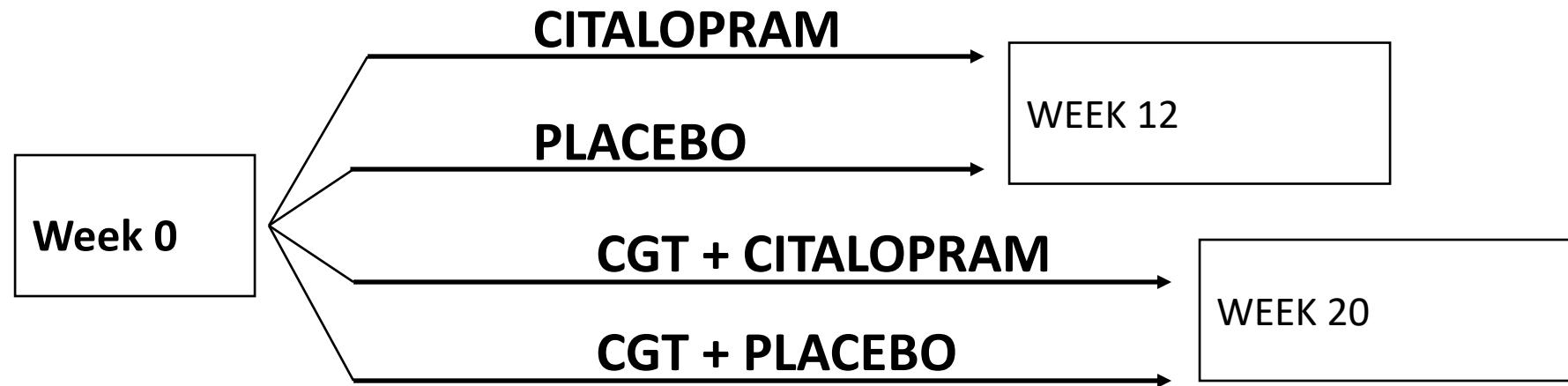
MGH

University of Pittsburgh

UCSD

STUDY DESIGN: 2X2 Factorial Design

	MEDICATION	PILL PLACEBO	NO PILL
ACTIVE PSYCHOTX	CGT + ESC	CGT + PBO	CGT
PSYCHOTX CONTROL	Psychotx control + ESC	Psychotx control + PBO	Psychotx control
NO PSYCHOTHERAPY	ESC	PBO	WAITLIST



CGT = Complicated Grief Therapy

ESC = antidepressant medication treatment

Study Aims:

- 1) To determine antidepressant efficacy by comparing citalopram vs pill placebo
(efficacy of MED vs Placebo)
- 2) Determine antidepressant efficacy when administered with CGT (efficacy of CGT+MED vs CGT)
- 3) Determine whether patients treated with citalopram benefit from addition of CGT
(effectiveness of GGT, compares MED+CGT vs MED)

Primary Outcome:
CG-Anchored
Clinical Global Impression-Improvement
Scale (CG-CGI-I):

Responder: CG-CGI-I of 1 or 2

- 1) Very Much Improved – Compared to baseline: clear evidence distress and impairment from CG is markedly improved. Patient feels very differently about role grief plays in her/his life.

- 2) Much Improved –Compared to baseline, distress and impairment from CG are definitely improved, and improvement is clinically significant. Patient notices some difference in role grief plays in her/his life.

Data analyzed based on
intention-to-treat (ITT) principle

Inverse probability weighting (IPW) used to adjust for
missing assessment at week 12.

Weighted logistic regression model used to estimate:
Response Rates
Relative Risk (95% CI)
p-value

Number needed to treat (NNT)

$1/(CIT \text{ response rate} - Placebo \text{ response rate})$

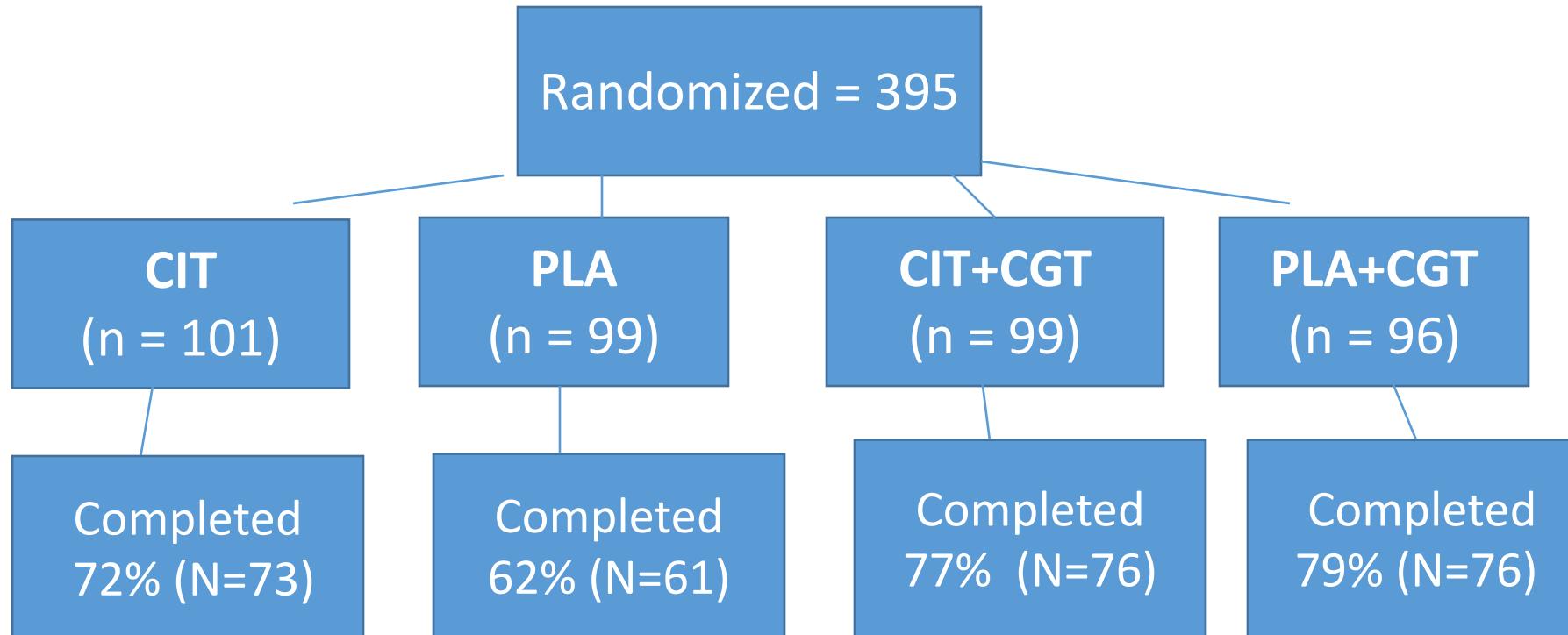
= An estimate of the number of patients we need to treat with CIT instead of Placebo in order to obtain one additional responder

Pre-Registration and Documentation to Ensure Reproducibility

Document the study protocol including primary outcomes, study aims, statistical analysis etc.

<https://clinicaltrials.gov/ct2/show/NCT01179568?type=lntr&cond=grief&draw=2&rank=9>

ASSESSMENT COMPLETION



STUDY PARTICIPANTS (N=395)

Age M (SD)	53.0(14.5)
Gender N (%)	
Female	308(78.0)
Race N (%)	
White	325(82.3)
Black	39(9.9)
Others	31(7.8)
Hispanic N (%)	45(11.4)

Education level N (%)

High School or Less	45(11.4)
Some College	139(35.2)
4 year College Degree or More	211(53.4)

Marital status N (%)

Never married	97(24.6)
Married	92(23.3)
Separated/divorced	68(17.2)
Widowed (not remarried)	138(34.9)

Person who died N (%)

Partner	144(36.5)
Parent	113(28.6)
Child	80(20.3)
Other relative or friend	58(14.7)

Time since loss M(SD) 4.7(7.2)**Violent death N(%)** 132(33.4)

MDD current N(%)	262(66.3)
PTSD current N(%)	154(39.0)

CGI severity rating N(%)

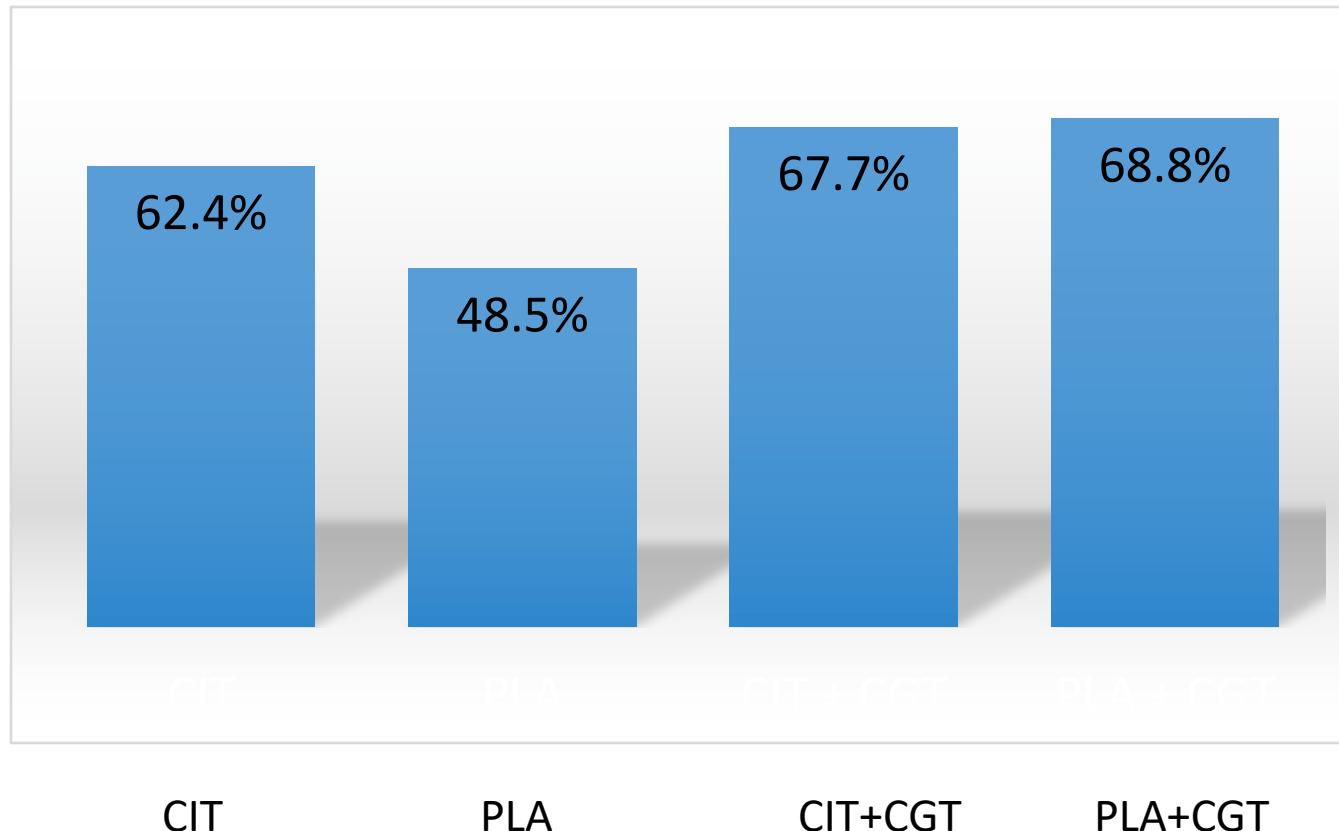
Mildly/Moderately ill	130(32.9)
MARKEDLY ILL	199(50.4)
SEVERELY/extremely ill	66(16.7)

Since death wish to be dead N(%)	221(55.9)
Since death non-specific active suicidal thoughts N(%)	103(26.1)

HOW STUDY OPTIMIZED PHARMACOTHERAPY

- Flexible dosing citalopram 10-40mg/day
- CG-informed clinical management
- Pharmacotherapy manual and safety rules
- Training and ongoing supervision
- Highly supportive clinic staff
- Open medication for participants who discontinued study treatment

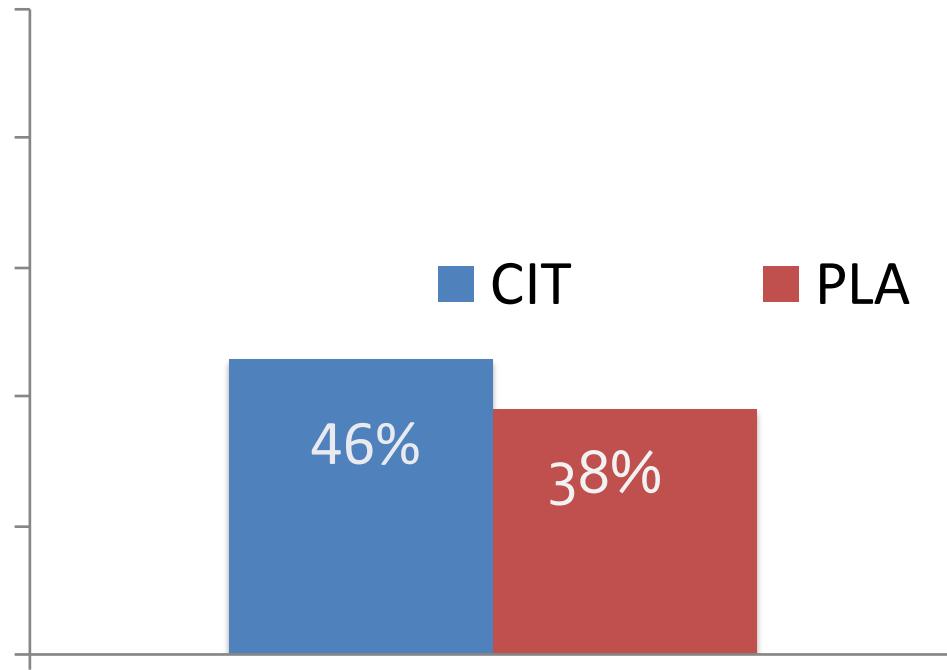
Medication Treatment Completion Rates



HEAL Study: Main Outcome (responder status)

Results Aim 1 (Efficacy):

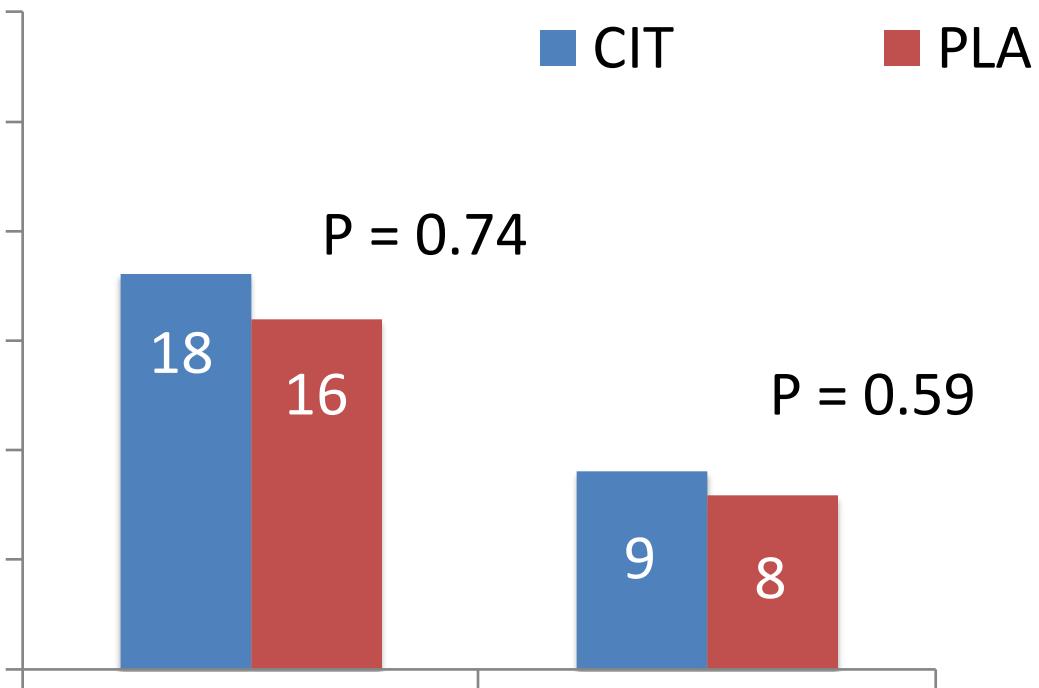
CIT vs Placebo in Meds only group



RR=1.21, CI: (0.82-
1.81), p=0.35 NNT =
12

HEAL Study: Symptom and Impairment Results

Aim 1 (Medication Alone Efficacy)

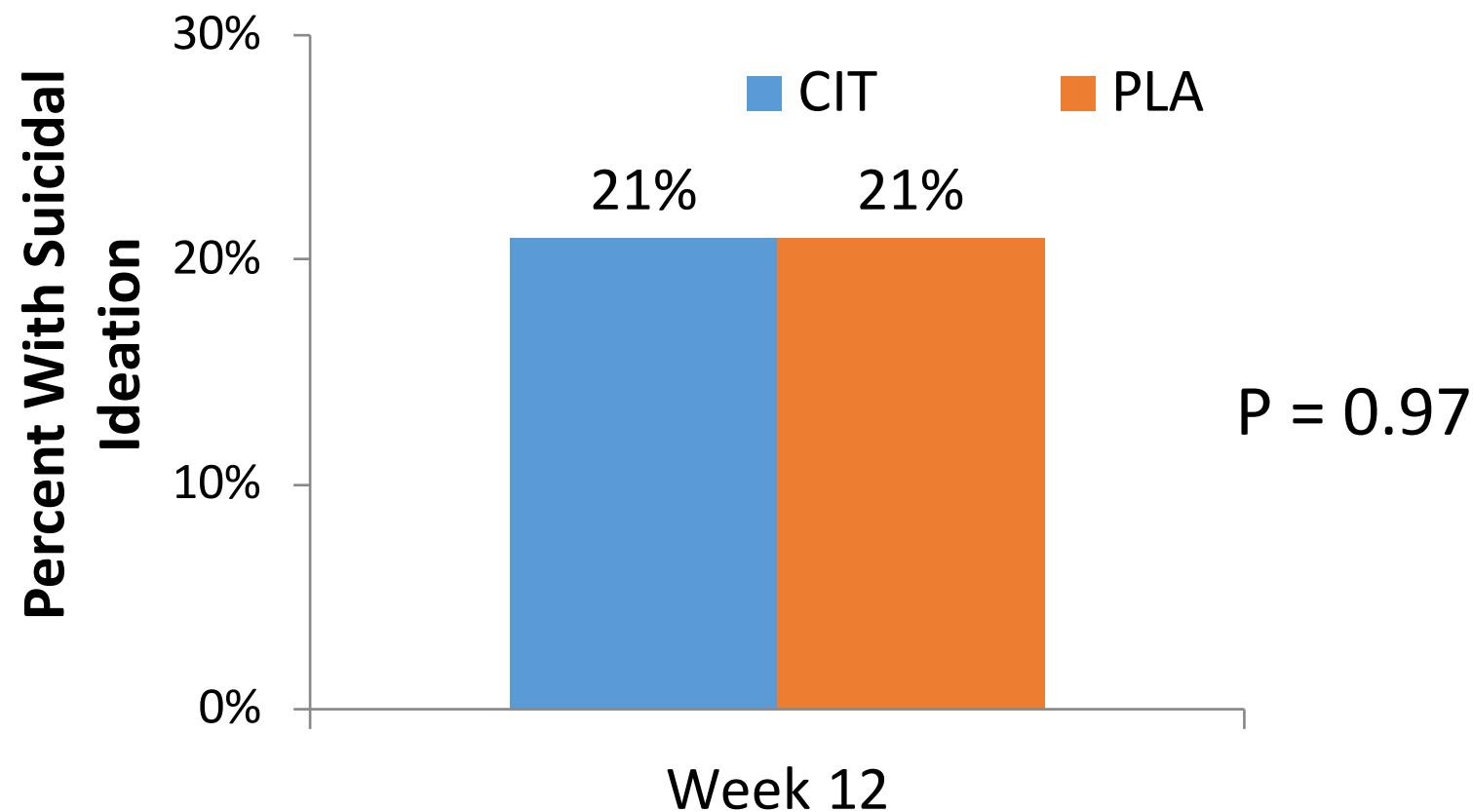


ICG: Inventory of Complicated Grief

WSAS: Work and Social Adjustment Scale

HEAL Study: Suicidal Thinking Results

Aim 1 (Medication Alone Efficacy)



Conclusion

Counter to hypotheses:

The HEAL study failed to find significant effects of citalopram compared to pill placebo (46% vs 38%, RR=1.21, CI: [0.82-1.81], p=0.35) at primary endpoint (12 weeks).

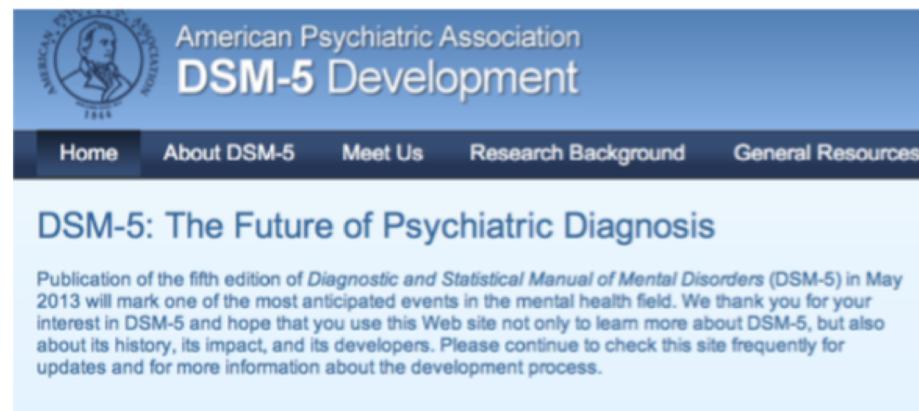
HOWEVER...

- While these data do not support the use of antidepressants as a primary treatment for patients with CG, Aim 1 did not examine effects as augmentation to CGT
- Future analyses will examine role of medication on comorbid depression

Original Statistical Research Motivated from HEAL

- Wang Y, Chen H, Zeng D, Mauro C, Duan N, Shear K. (2013). Auxiliary Marker-Assisted Classification in the Absence of Class Identifiers. *JASA*, 108(502): 553-565

Motivated by recent debates on introducing CG to 5th edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5).



Diagnosing a disorder from a list of symptoms.

- Traditional: clinical prototypes and communicated descriptively (DSM I, II, III, IV)
- Modern: empirical evidence and data-driven (Launch and Methodology Conference 2004, Kraemer et al. 2007)