



# Addressing Depression and Pain Together in Late-Life: The ADAPT Clinical Trial for Older Adults with Depression and Chronic Low Back Pain

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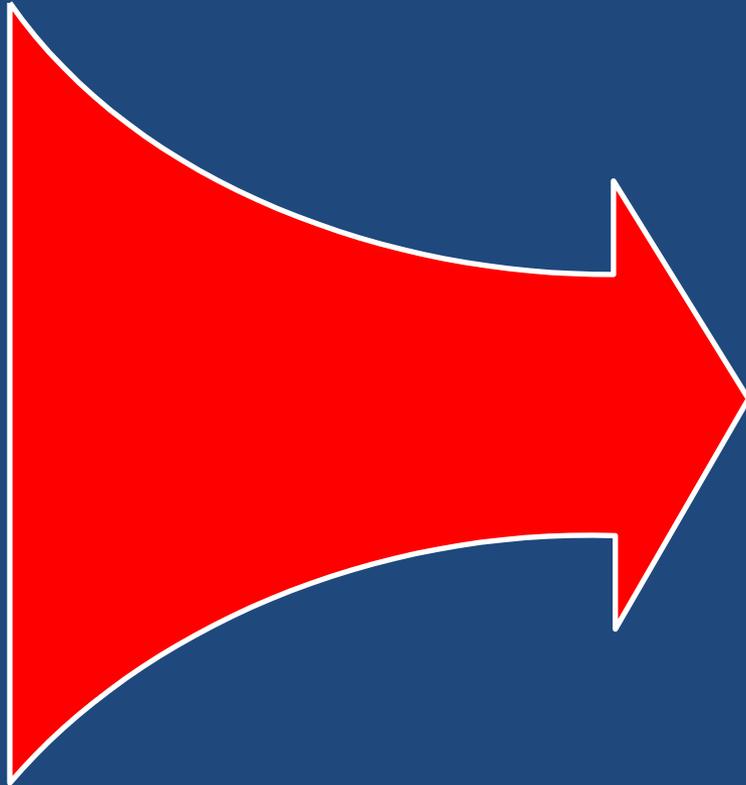
# Disclosure

- Receipt of Medication Supplies for investigator initiated trials from:
  - Pfizer
  - Reckitt Benckiser

# Outline

- Late-Life Treatment Resistant Depression (LL-TRD)
  - Scope of the Problem.
  - Pain: Contribution to treatment response variability.
- ADAPT
  - Design
  - Results
  - Conclusions

# Public Health Significance of Late-Life Depression

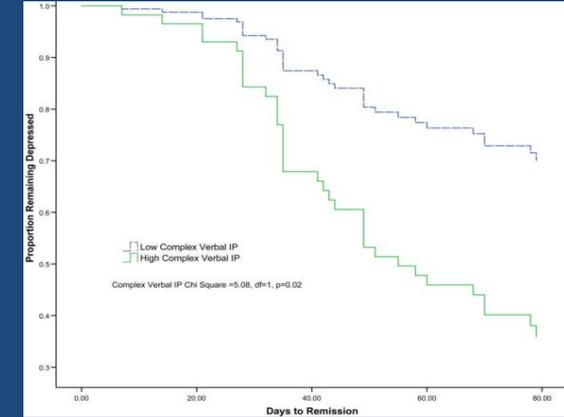
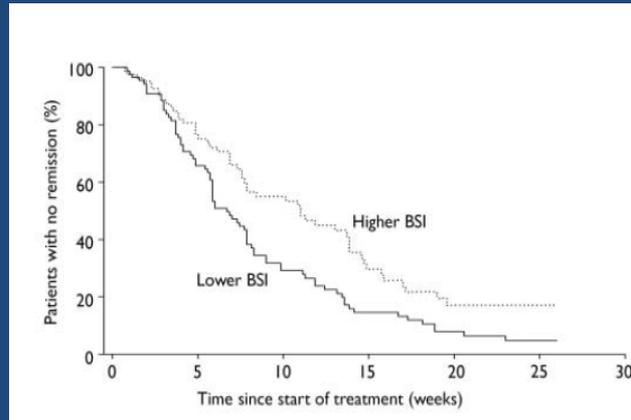
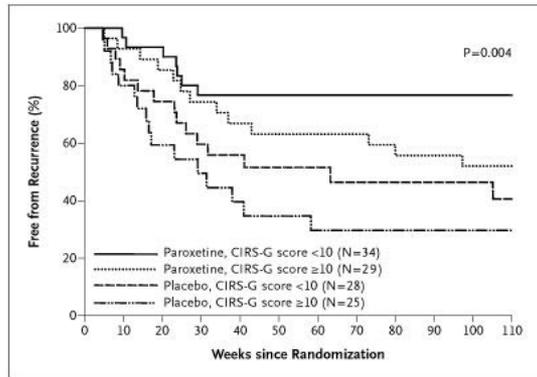


- ↑ healthcare utilization and costs
- ↓ quality of life
- poorer prognosis for comorbid conditions
- ↓ survival
- suicide

# Prevalence of LL-TRD

- 55-81% of LLD fail to remit with SSRI or SNRI.
- Little evidence to guide augmentation pharmacotherapy or psychotherapy.
- Replicated evidence in older adults support only lithium augmentation – ↓ tolerability.

# LL-TRD: The Rule, Not the Exception



## Medical Comorbidity

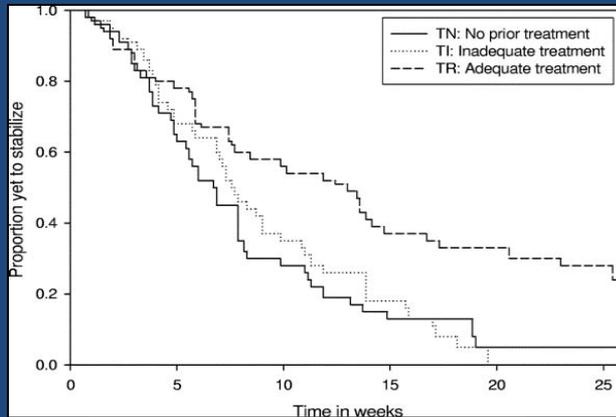
(Reynolds...  
Karp...Kupfer, 2006)

## Anxiety

(Greenlee, Karp et al 2010;  
Andreescu et al 2007)

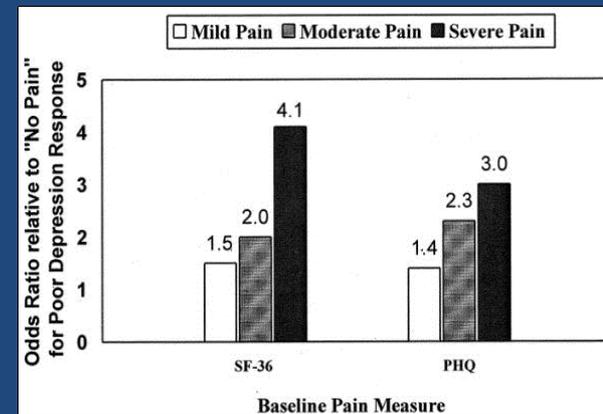
## Executive dysfunction

(Bogner et al, 2007)



## Treatment non-response

(Tew et al 2006)



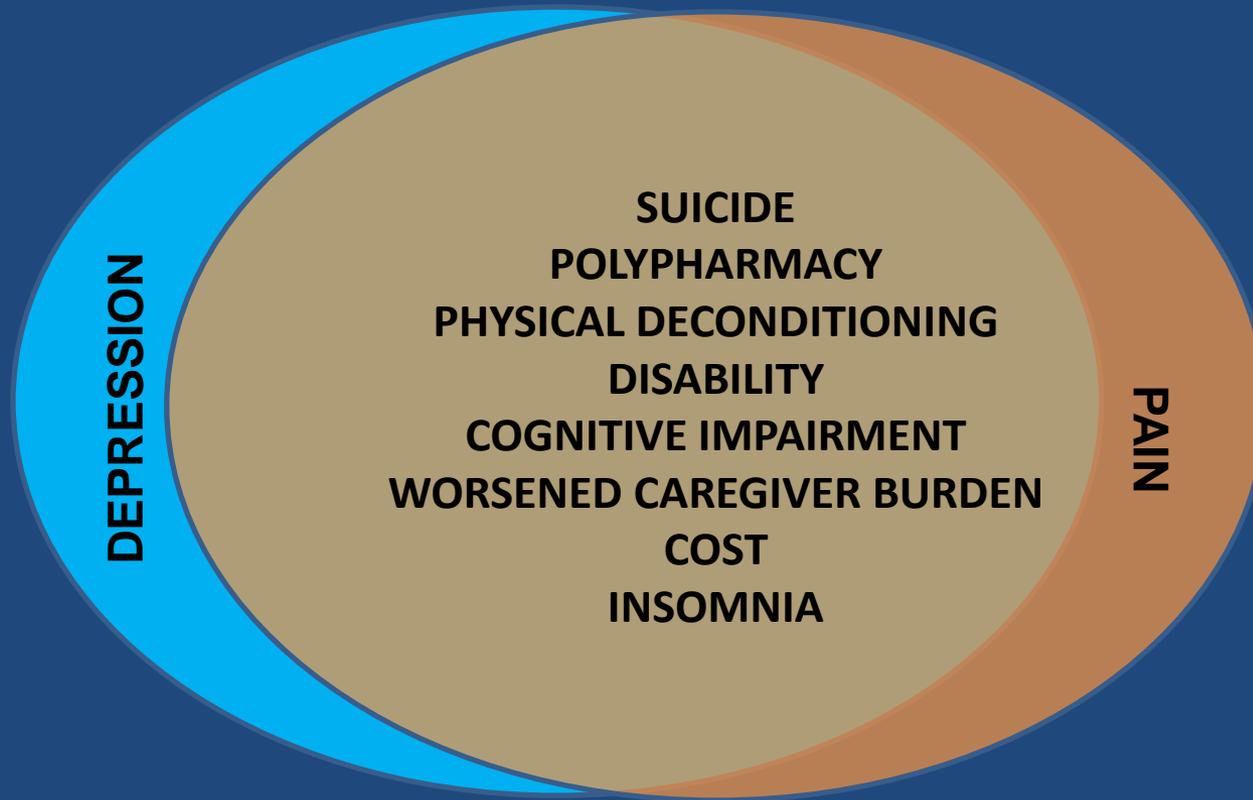
## Pain

(Bair et al 2004)

# Homoestasis and Homeostenosis

- Age-related impairments of homeostasis
  - Key principle of geriatrics
  - Homeostenosis: the inability to maintain homeostasis because of diminished resources.
- Both pain and depression are major contributors to homeostenosis in late-life.

# Pain and Depression: Overlapping Symptoms Support a Unified Approach to Treatment



Parsimonious approach to treatment is also based on shared:

- Biology (e.g., similar neurotransmitter and neuropeptide perturbation)
- Psychology (learned helplessness, low self-efficacy)

# Prevalence and Complications of Pain in Late-Life

- USA and Canada
  - 25–50% of community-dwelling older adults
  - 49–83% of nursing home residents report pain
- Chronic pain in late-life associated with
  - Anxiety and Depression *(Lenze, Karp, et al 2005; Casten et al, 1995)*
  - Functional impairment
  - Falls
  - Cognitive Impairment
    - Pain severity → executive dysfunction
    - Opioid use → worsens memory

*(Karp et al, 2006)*

# Chronic Low Back Pain (CLBP) in Late-Life

- 12% prevalence in the community.
- Most common referral to pain clinic. (Karp et al 2009)
- ↓ performance of IADLs.
- Compared to knee arthritis, CLBP have
  - ↑ Catastrophizing
  - ↑ Passive coping skills
  - ↑ Fear avoidance beliefs
  - ↑ Depression
  - ↓ Pain self efficacy

*(Morone, Karp...Weiner 2009)*

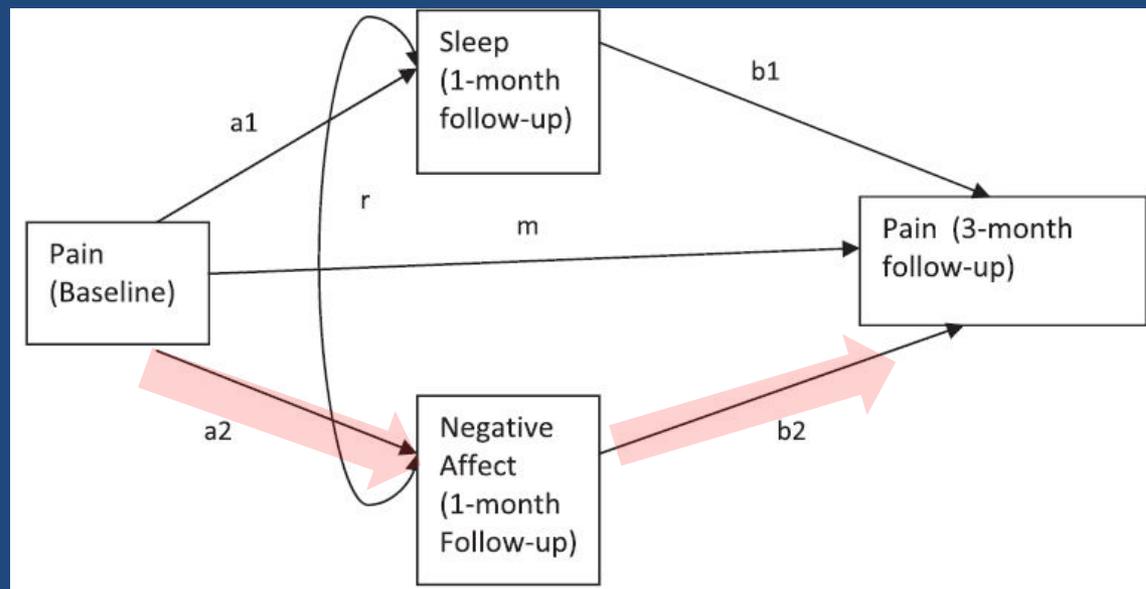
# Negative Affect and Sleep Disturbance May Be Associated With Response to Epidural Steroid Injections for Spine-Related Pain



Jordan F. Karp, MD,<sup>a,b</sup> Lan Yu, PhD,<sup>a</sup> Janna Friedly, MD,<sup>c</sup> Dagmar Amtmann, PhD,<sup>c</sup> Paul A. Pilkonis, PhD<sup>a</sup>

Time Point	Dependent Variable	Significant Independent Variable(s)	$\beta$	Individual $R^2$ (%)	Total $R^2$ (%)	
1	Back pain	NA	NA	NA	NA	
	Leg pain	NA	NA	NA	NA	
	RMDQ	Negative affect	.572	34.9	39.2	
		Relation status	.207	4.3		
	PROMIS pain behavior	Negative affect	.404	33.8	45.2	
		Education	-.200	6.2		
		Sleep	.212	2.6		
	PROMIS pain interference	Relation status	.165	2.6		
		Negative affect	.601	37.1	42.3	
		Education	-.182	2.8		
2	Back pain improvement	Sex	-.159	2.5		
	Leg pain improvement	Sleep	-.410	16.8	16.8	
	RMDQ	Sleep	-.338	11.4	11.4	
		Negative affect	.396	30.6	33.8	
	PROMIS pain behavior	Sleep	.239	3.3		
		Negative affect	.562	37.0	39.9	
	PROMIS pain interference	Relation status	.175	2.8		
		Negative affect	.615	37.8	37.8	
	3	Back pain improvement	Sleep	-.439	16.4	19.7
		Leg pain improvement	Age	-.184	3.3	
RMDQ		Sleep	-.376	14.1	14.1	
		Negative affect	.233	31.0	40.4	
PROMIS pain behavior		Sleep	.313	3.6		
		Global health	.214	3.4		
		Age	.158	2.4		
PROMIS pain interference		Sleep	.596	45.4	48.7	
		Global health	.198	3.3		
PROMIS pain interference		Sleep	.413	41.5	46.1	
	Negative affect	.314	4.5			

Abbreviation: NA, not applicable.



Negative affect influences functioning (but not pain) three months after ESI



**adapt**

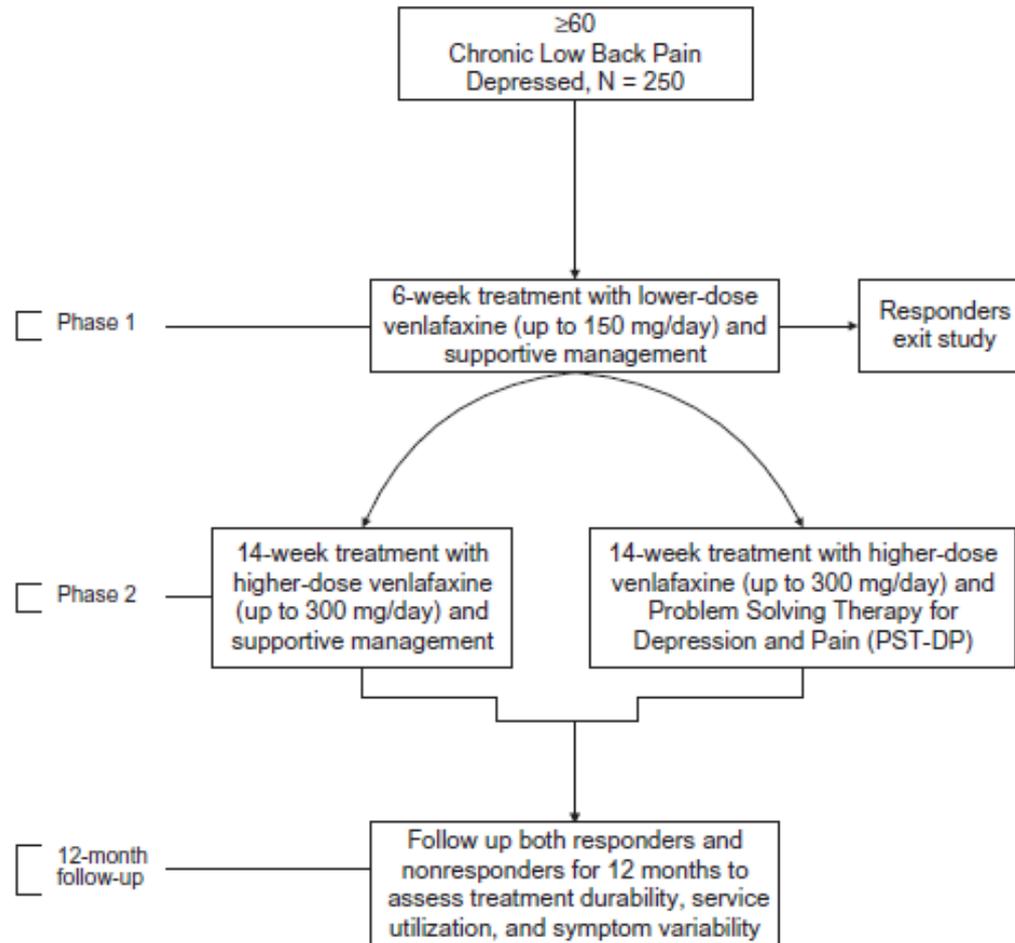
**addressing depression  
and pain together**

# ADAPT

- Stepped care approach for type of patient seen in 1<sup>o</sup> care.
  - Older adults
  - Depression
  - CLBP (failed previous treatments)
- Testing utility of augmentation psycho-tx for non-responders.
- Primary aim:
  - Compare combined high-dose venlafaxine with problem solving therapy for depression and pain (PST-DP) with high-dose venlafaxine with supportive management.
  - Outcomes: Depression/Pain and Disability.

**Original Research Articles**

**Addressing Both Depression and Pain in Late  
Life: The Methodology of the ADAPT Study**



Response = PHQ-9  
≤ 5 AND ≥ 30%  
improvement on NRS

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≤ 5 AND ≥ 30%  
improvement on NRS



# Recruitment from Primary Care

**Crayon, Aqua** Age Sex DOB MRN Allergies PCP Alerts Home Ph  
69 yea F 7/5/1941 076039695 Penicillins (None) HM 412-351-...

Place orders (Enc Date: 8/26/2010) - Wt: (Not entered for this visit) Ht: (Not entered for this visit)

Association CodeSearch Pref List SmartSets Pharmacy Providers CC Results Open Orders Pend Orders Sign Orders Verify Rx Benefits Referenc

New order:  Search  Both  Medication  Procedure

Order defaults: Not using defaults

**BestPractice Alert - Crayon,Aqua**

RESEARCH (1 Alert)

▼ Your patient may be eligible to participate in one of several studies of chronic low back pain and/or depression. Is it OK with your patient if a member of the study contacts him/her by telephone to assess their eligibility to participate? If YES, please click ACCEPT and complete the Smartset. (741)

Open SmartSet: Adapt Back Study

Diagnoses Associate... Level of service:

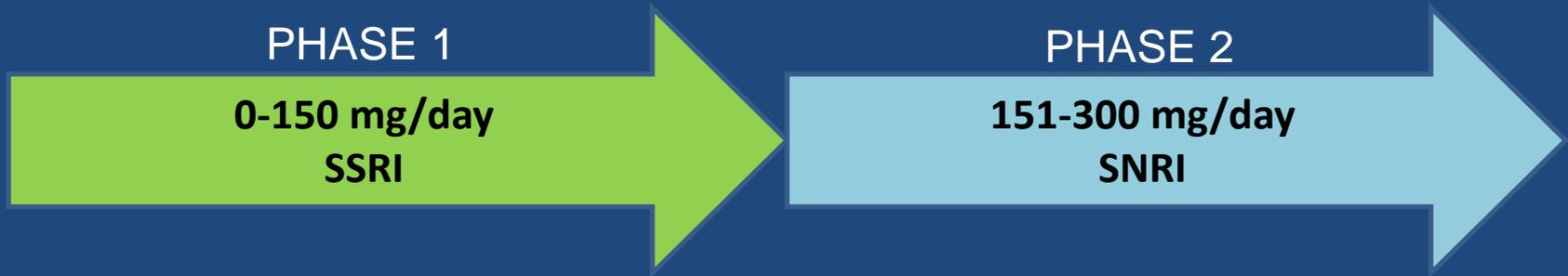
Add Diagnosis  Edit Remove   Show Resolve

P: Diagnosis Code Link Problem C

Subjects who signed consent (n=263):  
Referrals from EPIC BPA: 71 (27%)  
Other referrals: 192 (73%)

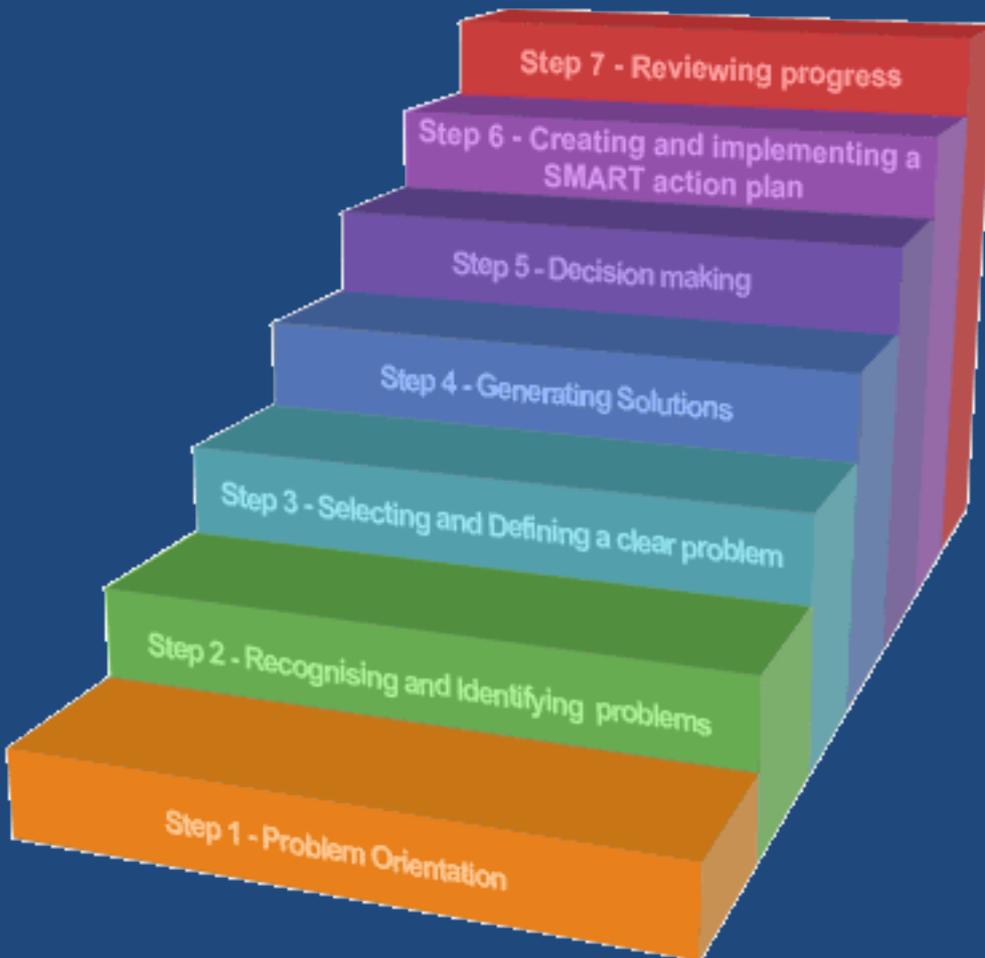
# Interventions

# Venlafaxine



- Reuptake inhibition of norepinephrine may lead to further antidepressant effect as well as enhanced analgesia.
- 150–225 mg/day for activity-limiting osteoarthritis reduces pain intensity and improves function.

# 7 Steps of PST



- If solutions selected by patient, may spend time on:
  - Activity and movement scheduling
  - Brief behavioral treatment of insomnia (BBTI)
  - Relaxation techniques
  - More effective use of analgesics

# Active Control: Supportive Medication Management

## PERMITTED INTERACTIONS

Reassurance to take medication in spite of mild but anxiety-provoking side effects.

Support in the face of criticism by others who communicate negative attitudes about treatment for depression.

Conveying a sense of hope and optimism throughout all phases of treatment.

Education and information giving about the characteristics of venlafaxine and the reasons it is considered safe and effective in the treatment of LLD and CLBP. Side effects are discussed and managed.

Instruction, education, and information giving about CLBP and a discussion of next-step possible treatments.

Simple advice on what patients can do to help themselves (e.g., avoidance of stressful situations).

Encouragement of ventilation of depressive feelings (including about residual symptoms and suicidal ideation)

## FORBIDDEN INTERACTIONS

Focusing on cognitive distortions, catastrophizing, interpersonal relationships.

Sequential problem solving.

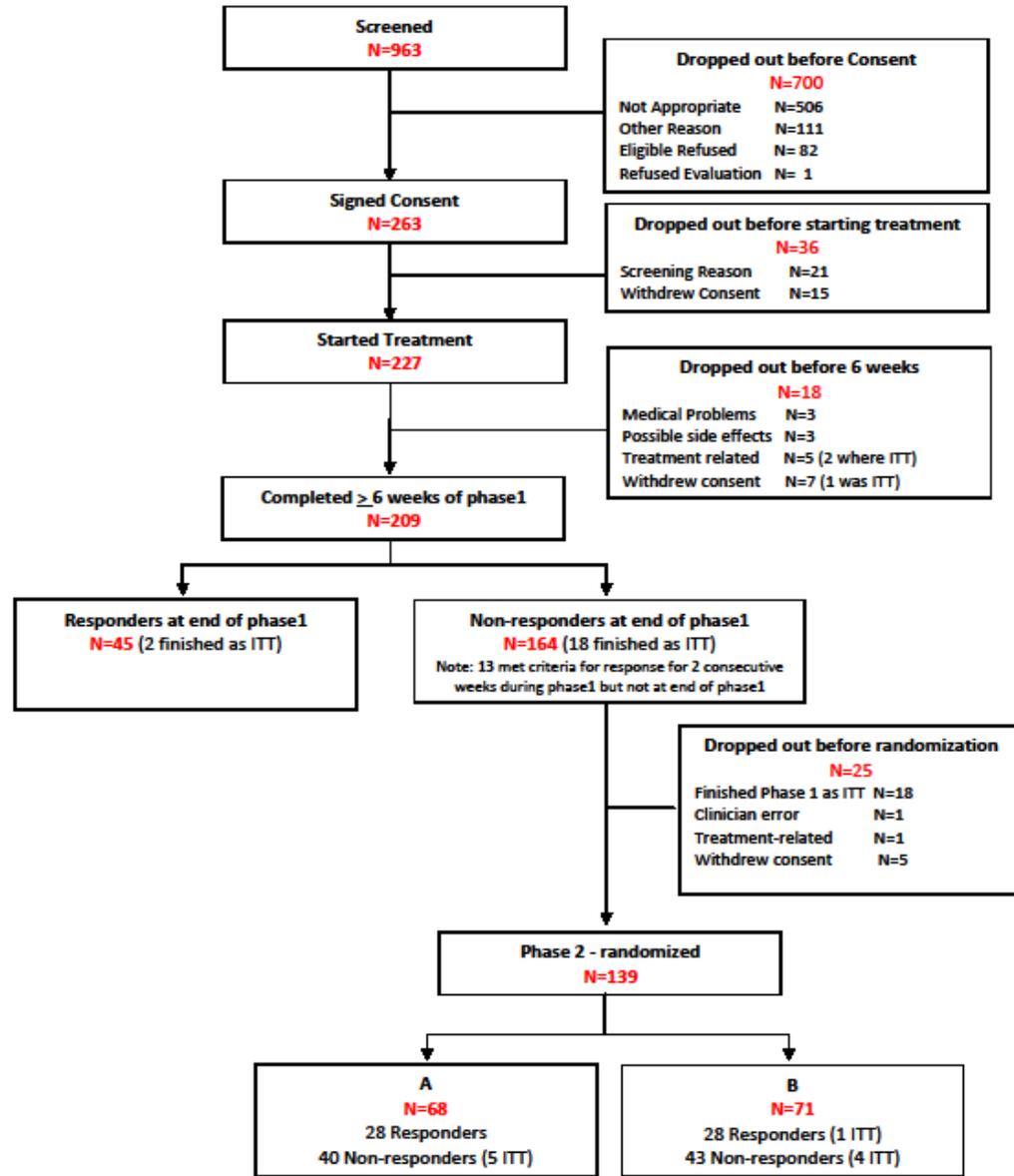
Interpretation of interpersonal events or styles of relating or clarification of feelings towards others.

Interpretations relating to recent losses, secondary gain, or other psychological mechanisms.

Specific behavioral instructions or routines other than simple advice about activity.

Explanations of the psychodynamics of depression.

# ADAPT Consort Diagram



Signed consent/screened: 27%

Started treatment/signed consent: 86%

Completed phase 1/ started treatment: 92%

Randomized/phase 1 non-responders: 85%

10% dropout phase 2

\*14 dropped out during phase 2  
 \* A: N=8/68, 11.76% (Medical problems=3, treatment related =2, withdrew consent=3)  
 \* B: N=6 /71, 8.45% (Medical problems = 1, treatment related = 3, withdrew consent =2)

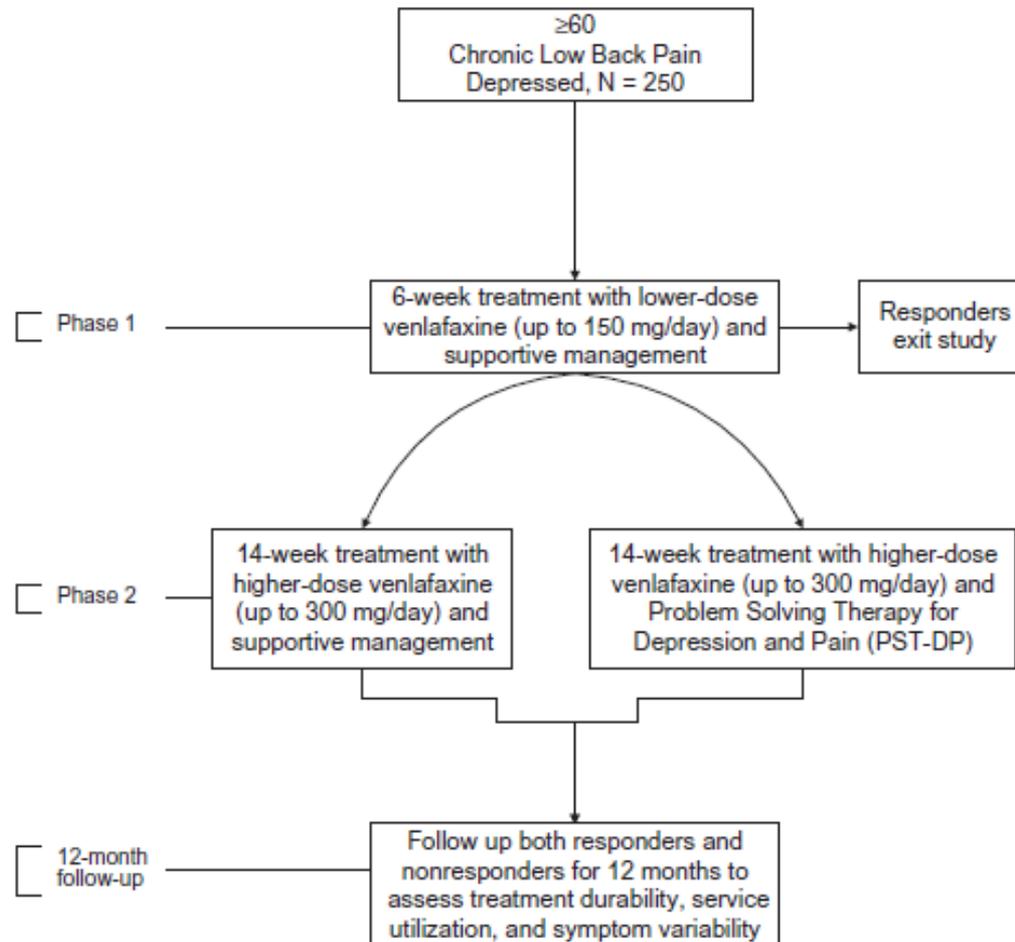
Dropout or switching to ITT during phase 2 (A:11/68 vs. B 11/71, Fisher exact p=0.99).

Baseline Characteristics	Phase 1 Responder (n=45)	Phase 1 Non-responder (n=164)	
Age	70.2 (7.5)	<b>70.5 (8.5)</b>	F(2,224)=0.30, p=0.74
% Female	60	<b>61</b>	Chisq(2)=0.01, p=0.99
%AA/%White	8.9/91.1	<b>13.4/84.8</b>	Fisher exact p=0.05
Education	14 (2.9)	<b>14.1 (2.7)</b>	F(2,224)=0.12, p=0.88
Cumulative Illness Rating	10.2 (3.1)	<b>11.7 (4.4)</b>	F(2,223)=4.17, p=0.02 NR > R
BMI	31.1 (6.1)	<b>30.3 (6.6)</b>	F(2,216)=0.44, p=0.64
% Fibromyalgia	18.6	<b>31.9</b>	Chi sq(2)=4.25, p=0.12
% Spine surgery	24.4	<b>37.8</b>	Chi sq(2)=3.17, p=0.20
PHQ9	14.3 (3.4)	<b>16.5 (4.2)</b>	F(2,224) = 5.68, p=0.004 NR > R
% Antidepressant Treatment History Form (ATHF) $\geq 3$	18.4	<b>55.3</b>	Chisq(2)=16.82, p=0.0002 NR > R
Pain NRS	11.2 (3.2)	<b>11.9 (2.9)</b>	F(2,223)=0.82, p=0.44
Pain Map	9.2 (5.4)	<b>13.5 (9.3)</b>	F(2,218)=4.75, p= 0.010 NR > R
Roland Morris Back Disability Questionnaire	12.87 (4.6)	<b>15.61 (4.0)</b>	F(2,224)=7.54, p=0.0007 NR>R

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# Making Use of Phase 1 Data

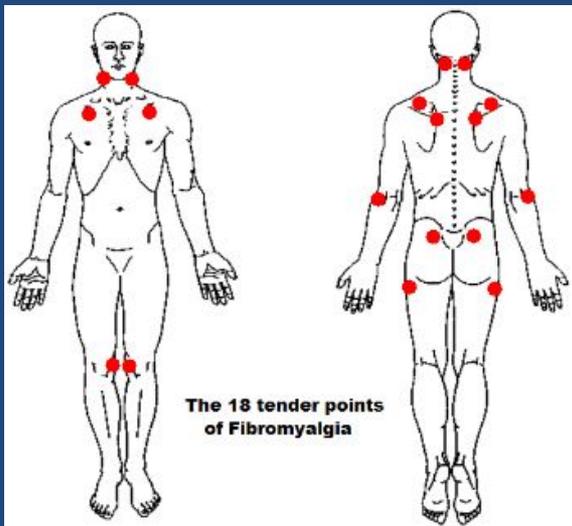


*Original Research Articles*

Treating Concurrent Chronic Low Back Pain and Depression with Low-Dose Venlafaxine: An Initial Identification of “Easy-to-Use” Clinical Predictors of Early Response

Predictor	B	SE B	Odds Ratio for responding to both Depression and Pain at 6 Weeks	P value
Fibromyalgia	-0.51	0.58	0.60	0.38
Baseline anxiety	-0.38	0.31	0.68	0.22
Pain Map Score	-0.04	0.03	0.96	0.19
Baseline PHQ-9	-0.09	0.06	0.91	0.12
2-week change in NRS	-0.11	0.05	0.89	0.03

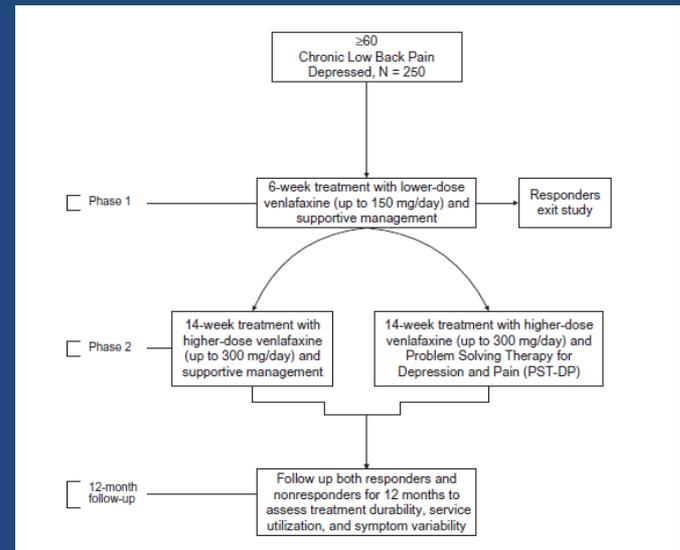
# Advancing the screening of fibromyalgia in late-life depression: practical implications for psychiatric settings



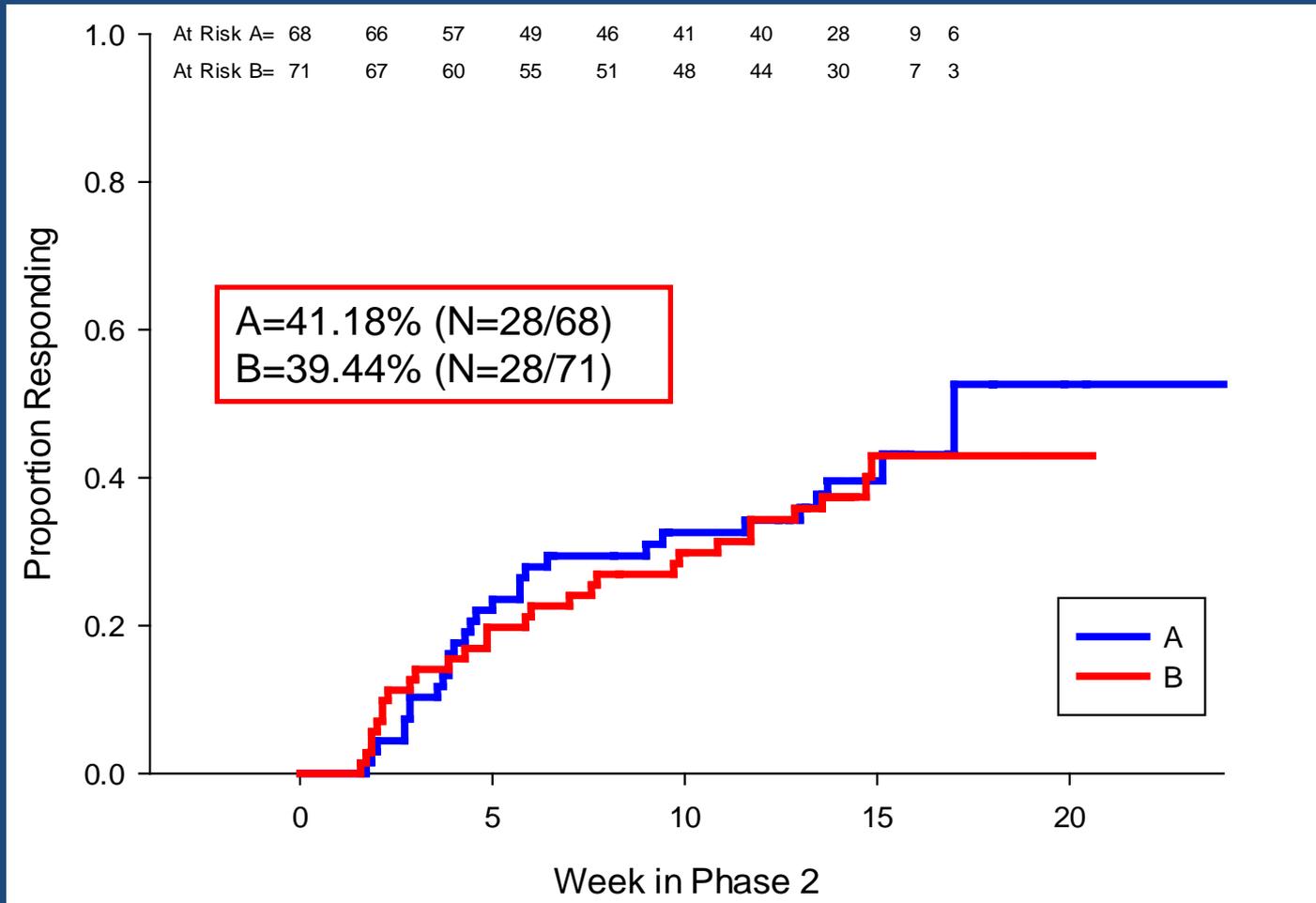
	Sensitivity	Specificity	PPV	NPV
Pain Map (>8)	0.93	0.46	0.42	0.94
“Do you often feel like you hurt all over?”	0.91	0.75	0.59	0.95

# Phase 2 Intervention

- Median dose venlafaxine: 244 mg/day
- Median maximum dose venlafaxine: 300 mg/day
- Average number of PST-DP or supportive management sessions:
  - Cell A: 8.4
  - Cell B: 9.2



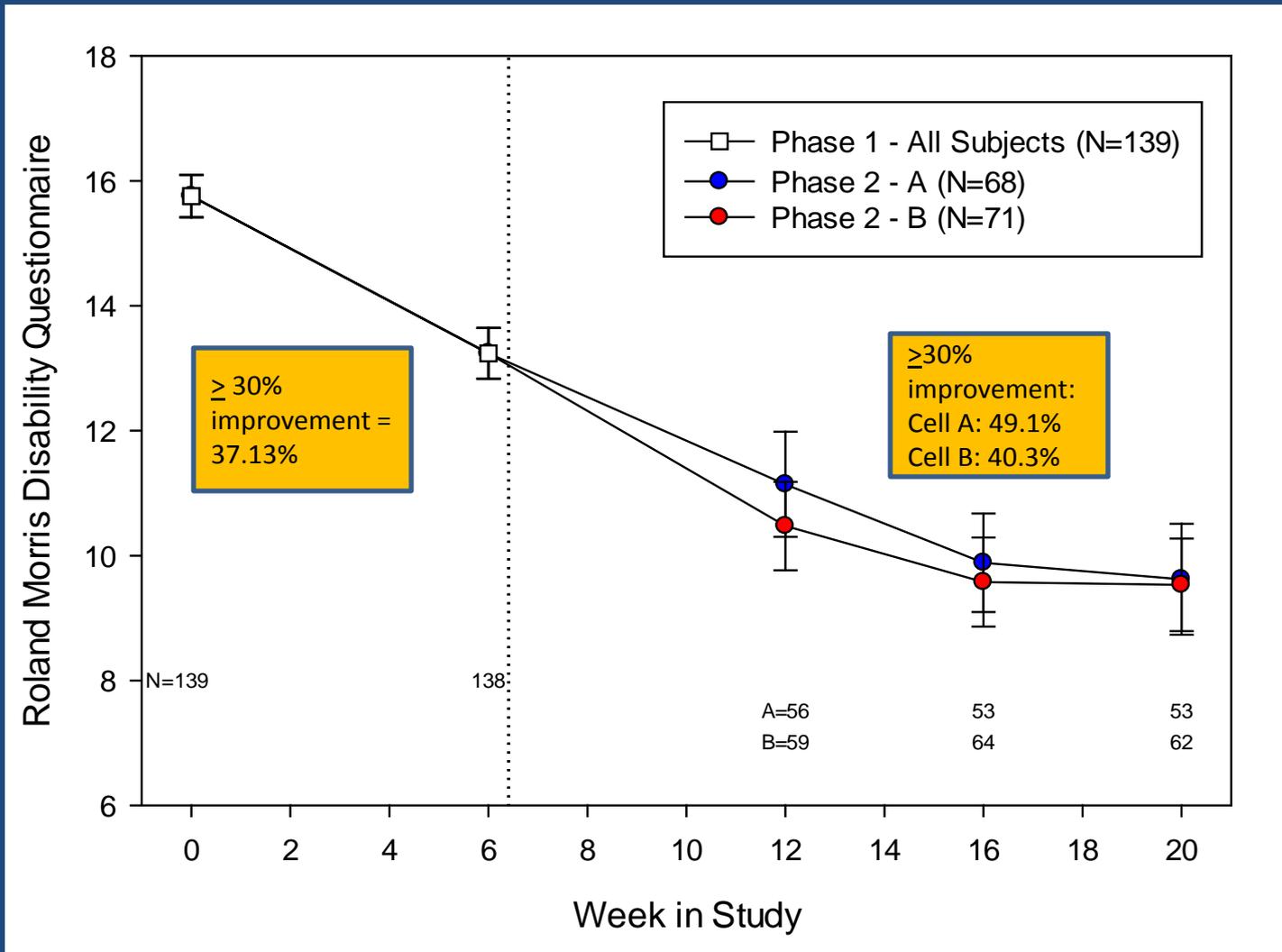
# Response: 2 Sequential visits of PHQ-9 $\leq 5$ and $\geq 30\%$ Reduction in NRS



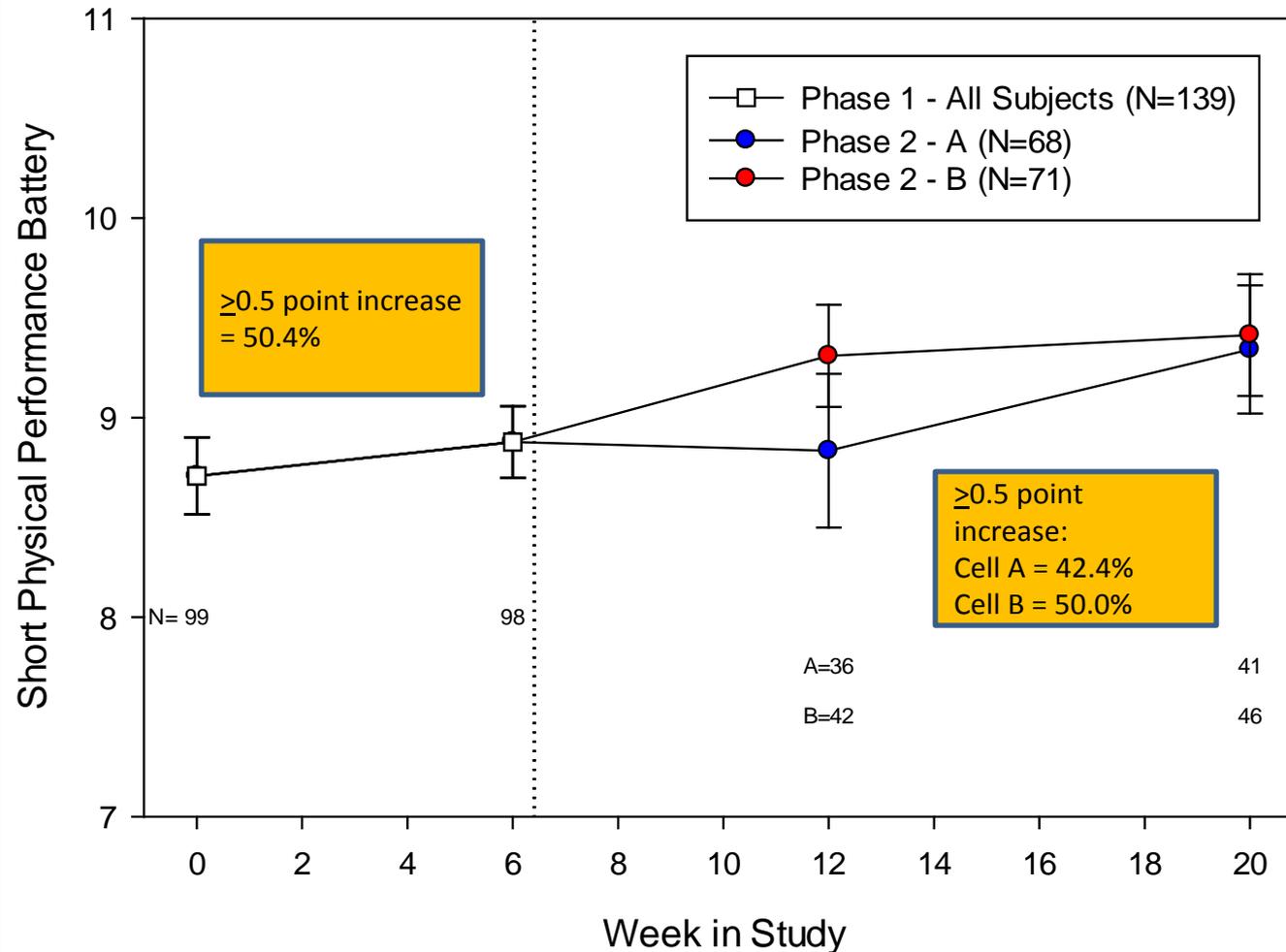
# Final Phase 2 Remission

	A	B	
	Final Remission % (N)	Final Remission % (N)	
Both Depression and Pain	30.88 (21/68)	18.31 (13/71)	Fisher exact p=0.11
Depression	44.12 (30/68)	32.39 (23/71)	Fisher exact p=0.17
Pain	42.65 (29/68)	46.48 (33/71)	Fisher exact p=0.73

# Change in Reported Low Back Disability



# Change in Observed Functioning: Short Physical Performance Battery



# ADAPT Conclusions (1)

- LL-TRD is the norm, not the exception.
- In ADAPT active phase, no added value of PST-DP.
  - ? Added value during 12 months of follow-up?
- Venlafaxine with SM, frequent contact, and measurement-guided care leads to significant response rates, especially for pain.

## ADAPT Conclusions (2)

- 40% bivariate response rate during phase 2.
- Cumulative improvement in disability.
- Lack of an effect may be due to comparison of two potent interventions.

# This Is a Group Effort

<b>Pitt Collaborators</b>	<b>Collaborators: Toronto and Washington U</b>	<b>Staff</b>	<b>Financial Support and Administration</b>
<b>CF Reynolds</b>	<b>Benoit Mulsant</b>	<b>Sunita Chickering</b>	<b>Kathy Slomka</b>
<b>Meryl Butters</b>	<b>Daniel Blumberger</b>	<b>Chloe Bolon</b>	<b>Doris Rubio and CTSI</b>
<b>Wahed Abdus</b>	<b>Eric Lenze</b>	<b>Jackie Stack</b>	<b>Hermi Woodward and OGC</b>
<b>Bruce Rollman</b>		<b>Liz Weber</b>	<b>NIA (PO: Wen Chen, PhD)</b>
<b>Debra Weiner</b>		<b>Amy Begley</b>	<b>NIMH (PO: Jovier Evans PhD)</b>
<b>Jen Morse</b>		<b>Salem Bensasi</b>	<b>NARSAD</b>
<b>Mark Miller</b>		<b>Sarah Walker</b>	
<b>Frank Lotrich</b>			
<b>MA Dew</b>			
<b>Ellen Frank</b>			
<b>Mark Richardson</b>			
<b>Avniel Ghuman</b>			
<b>Ajay Wasan</b>			
<b>Cheryl Bernstein</b>			