

Novel Approaches to Improving Medication Follow-Through and Outcomes

Dawn I. Velligan, PhD

*Professor, Department of Psychiatry,
Henry B. Dielmann Chair
University of Texas Health Science Center,
San Antonio
San Antonio, Texas*

Martha Sajatovic, MD

*Professor of Psychiatry and Neurology
University Hospitals Cleveland Medical Center
Case Western Reserve University,
School of Medicine
Cleveland, Ohio*

Faculty Disclosure

- **Dr. Sajatovic:** CME Activities—American Physician Institute, CMEology, Creative Educational Concepts, Global Medical Education, MCM Education, Potomac Center for Medical Education; Consultant—Bracket, Health Analytics, Janssen, Neurocrine, Otsuka; Grant/Research Support—Alkermes, Centers for Disease Control and Prevention, International Society for Bipolar Disorders, Janssen, National Institutes of Health, Otsuka, Reinberger Foundation, Reuter Foundation, Woodruff Foundation; Royalties—Johns Hopkins University Press, Oxford Press, Springer Press.
- **Dr. Velligan:** Consultant—Alkermes, Indivior, Janssen, Lundbeck, Otsuka; Grant/Research Support—Alkermes, Boehringer Ingelheim; Speakers Bureau—Janssen.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- List the ways in which adherence has been measured in published research and in clinical practice
- Describe at least 3 new technologies that could be applied to improving medication follow-through in real-world settings
- Identify at least 2 caveats in the use of new technologies to improve the regular taking of medication

Objectives

- The scope of the adherence problem and its consequences
- The definition and measurement of problems with medication follow-through
- New technologies that are changing the ways we learn about and improve medication follow-through
- Caveats to consider in the use of new technologies

The Problem of Medication Follow-Through

America's Other Drug Problem

“Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.”

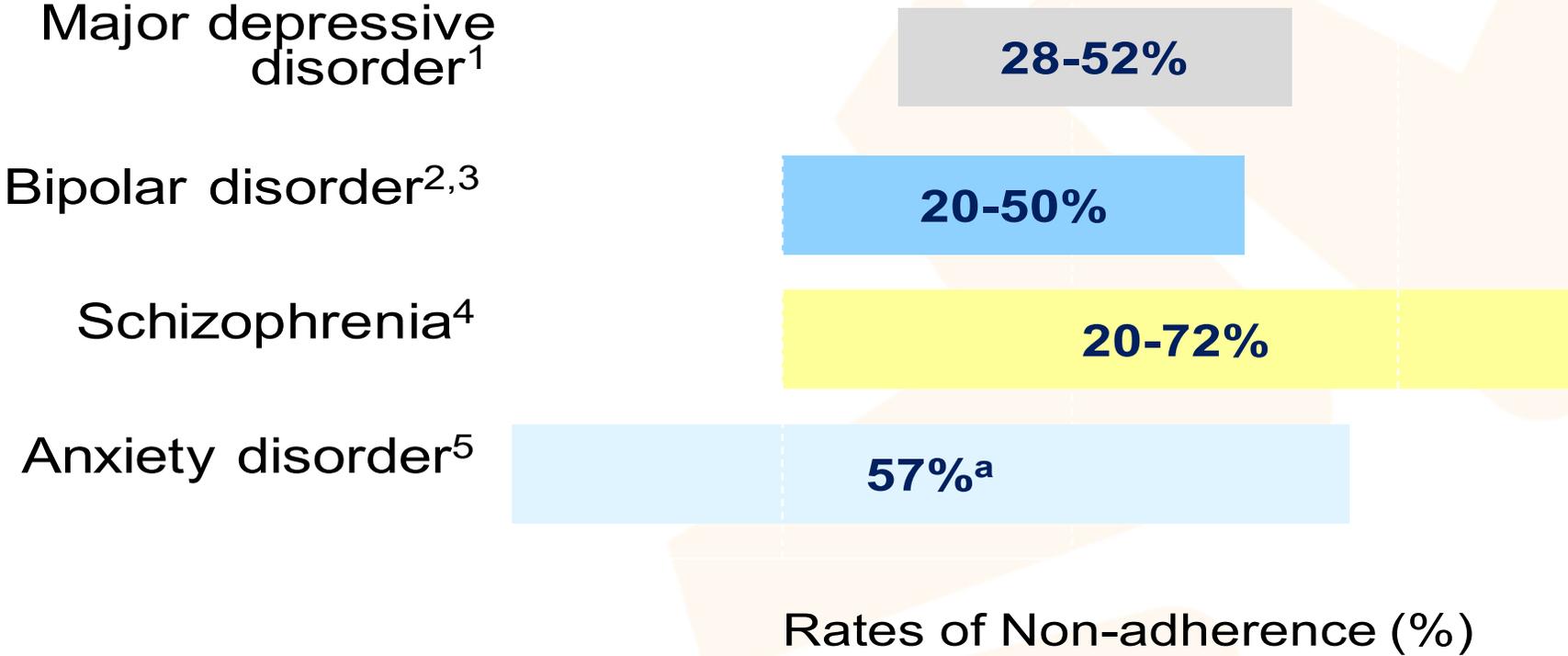
Haynes: Requoted in 2003 World Health Organization Report

The Problem of Medication Follow-Through



- Poor across physical and psychiatric disorders
- Particularly poor in persistent disorders where treatments are designed to prevent symptom onset or recurrence and when the consequences of stopping treatment are delayed
- Hospitalization, increased substance use, risk of suicide, illness progression, derailment of recovery, loss of employment, homelessness, criminal justice involvement

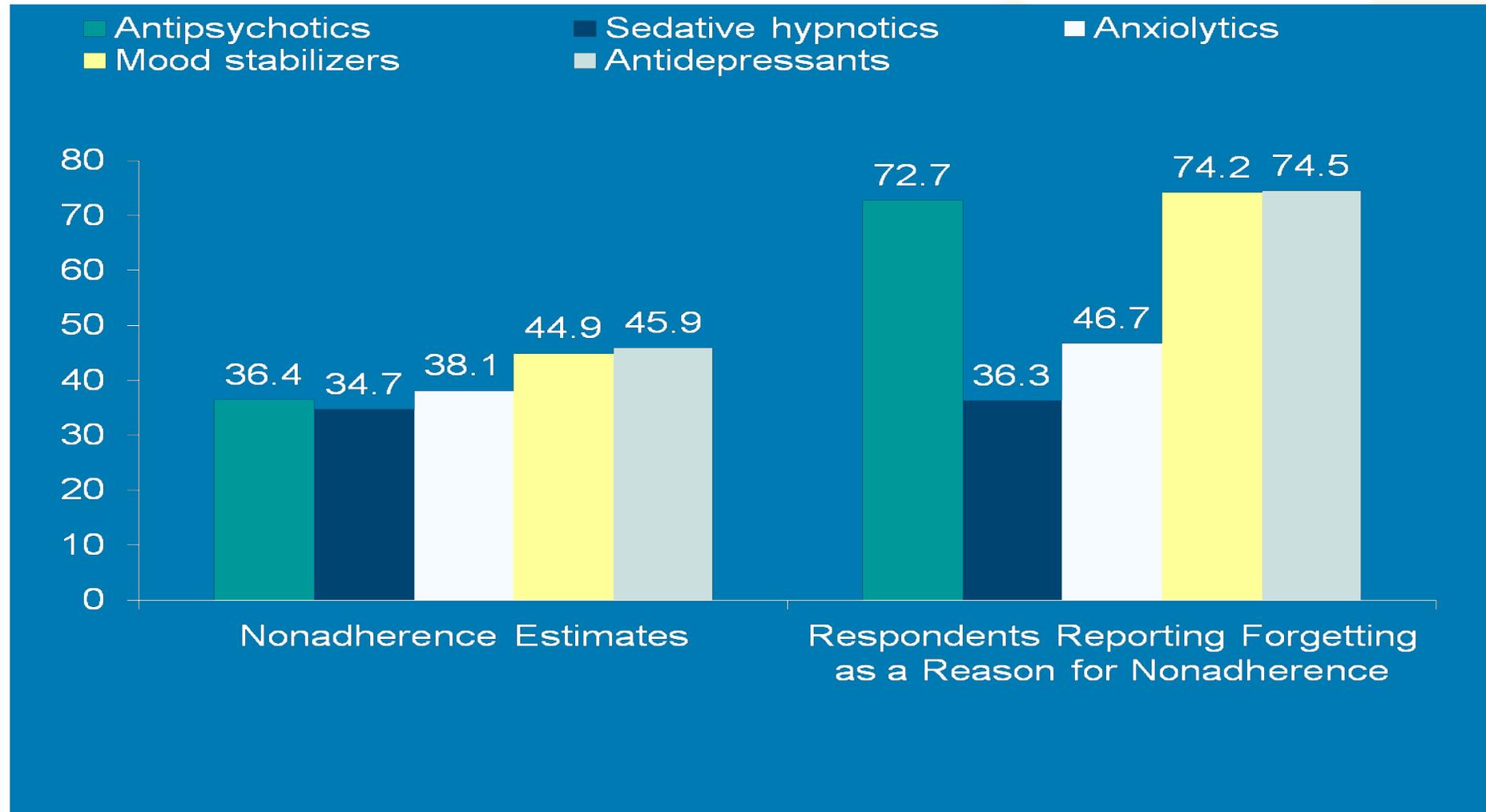
Rates of Nonadherence across Psychiatric Disorders



^aLimited data available.

Vergouwen AC, et al. *J Clin Psychiatry*. 2003;64(12):1415-1420. Scott J, et al. *J Clin Psychiatry*. 2002;63(5):384-390. Cochran SD. *J Consult Clin Psychol*. 1984;52(5):873-878. Lacro JP, et al. *J Clin Psychiatry*. 2002;63(10):892-909. Stein MB, et al. *Psychiatr Serv*. 2006;57(5):673-680.

Adherence Drug Variability



N=6201.

Bulloch AG, et al. *Soc Psychiatry Psychiatr Epidemiol.* 2010;45(1):47-56.

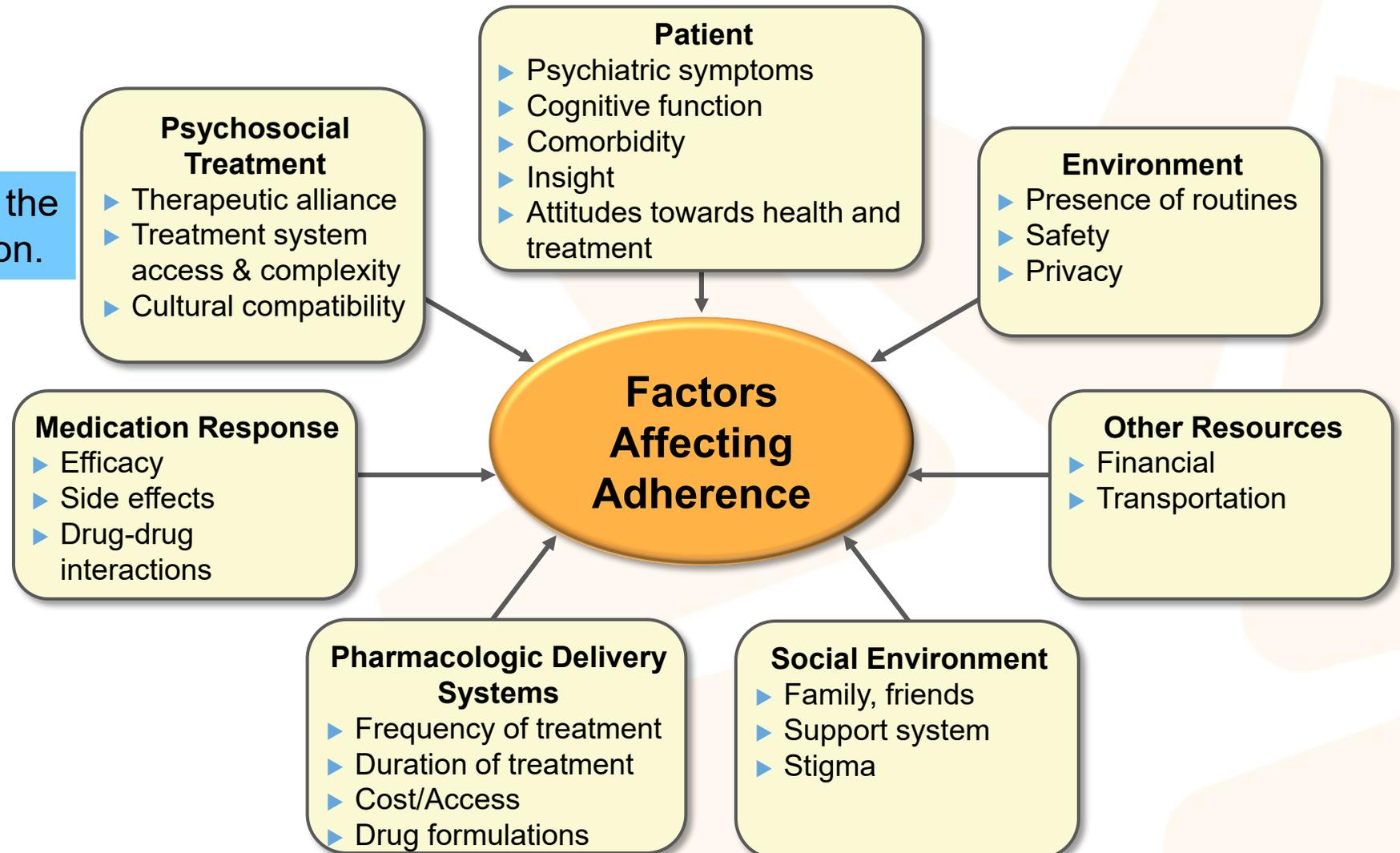
Health Care Consequences of Problem Adherence

- Causes 10% of total hospital admissions
- Causes 22% of nursing home admissions
- Has been associated with 125,000 deaths
- Results in \$100 billion/year in unnecessary hospital costs
- Costs the US economy \$300 billion/year



Multi-factorial Determinants of Problem Adherence

Interventions must address the determinants for each person.



Adherence Interventions Must Be Tailored to the Reasons for Problem Adherence

- For intentional adherence related to insight; focus is on therapeutic alliance and MI. Brief MI can be done in context of medication visits; it is a skill that can be trained and practiced
- Once motivation to take medication is present—you now may have to deal with unintentional adherence
- In order to partner with patients, it is important to understand what they believe medications do for them, not just why they don't like medication

What do you think medications are doing for you?

- Balancing/stabilizing mood (42%)
- Decreasing anxiety/depression (19%)
- Improving sleep (10%)
- Individuals mainly focused on need to manage depression

MI = motivational interviewing.

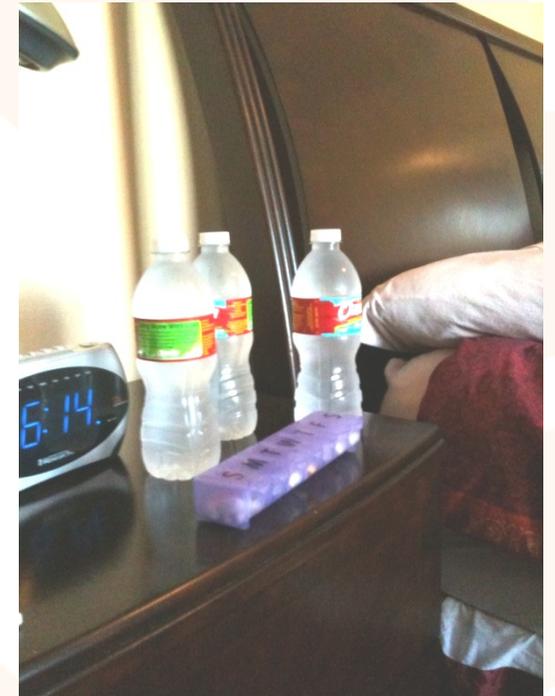
Sajatovic M, et al. *J Affect Disord.* 2009;115(3):360-366. Levin JB, et al. *CNS Drugs.* 2016;30(9):819-835.

Adherence Assessments Must Be Tailored to the Reasons for Problem Adherence

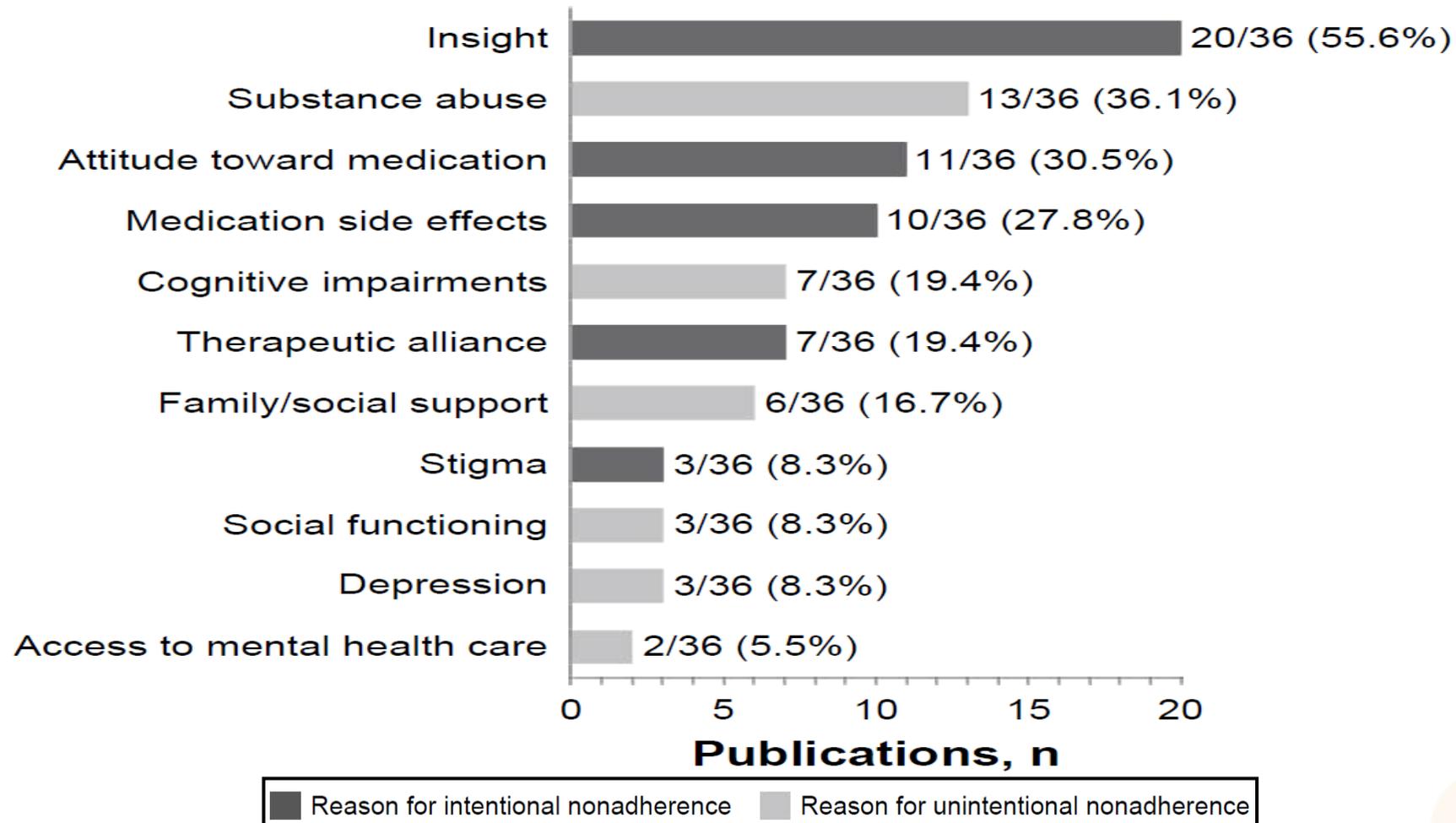
- For unintentional adherence related to problems with forgetting, distractibility, and lack of daily routine—reliable reminders in tune with the person’s specific life circumstances and environment are needed
- Reminders will do no good if the problem is side effects or finances and these are not addressed. Adherence intervention is not once size fits all

I forget my medications when I leave for work.

I forget my night medication every night. They are in the kitchen. I don't mean to?



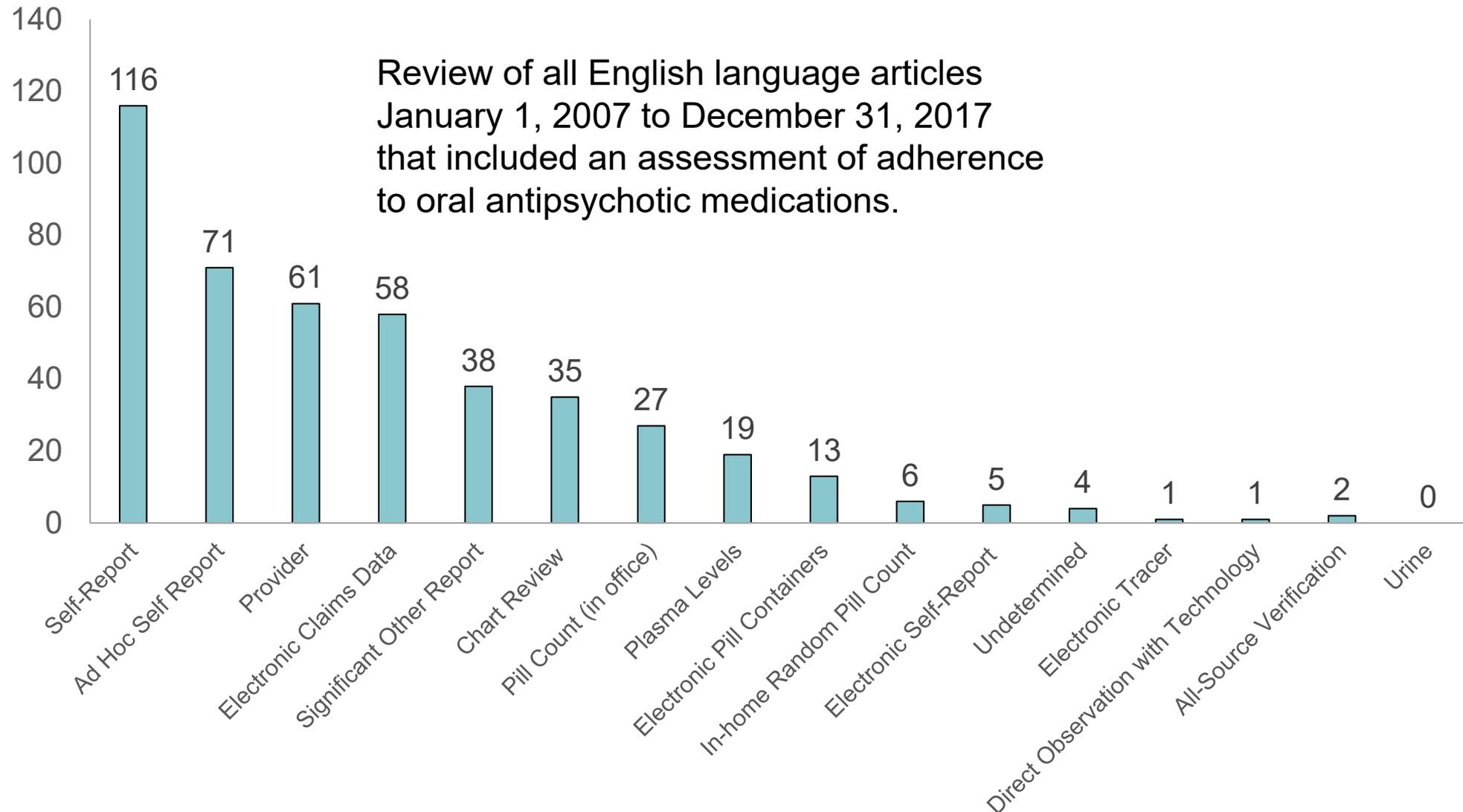
Top Reasons for Poor Antipsychotic Adherence



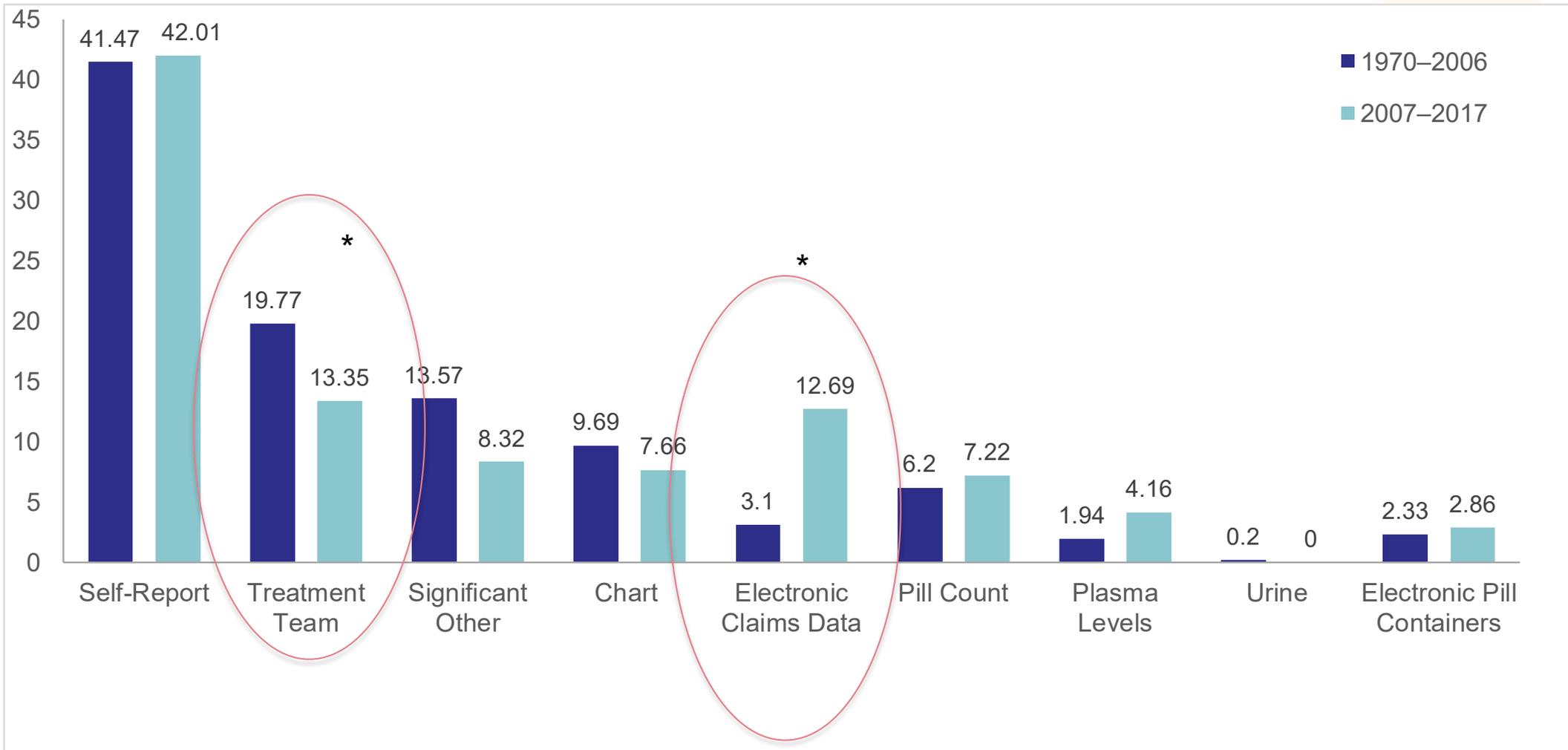
How Adherence is Measured

Are you taking your medication?

How Adherence is Assessed in Research

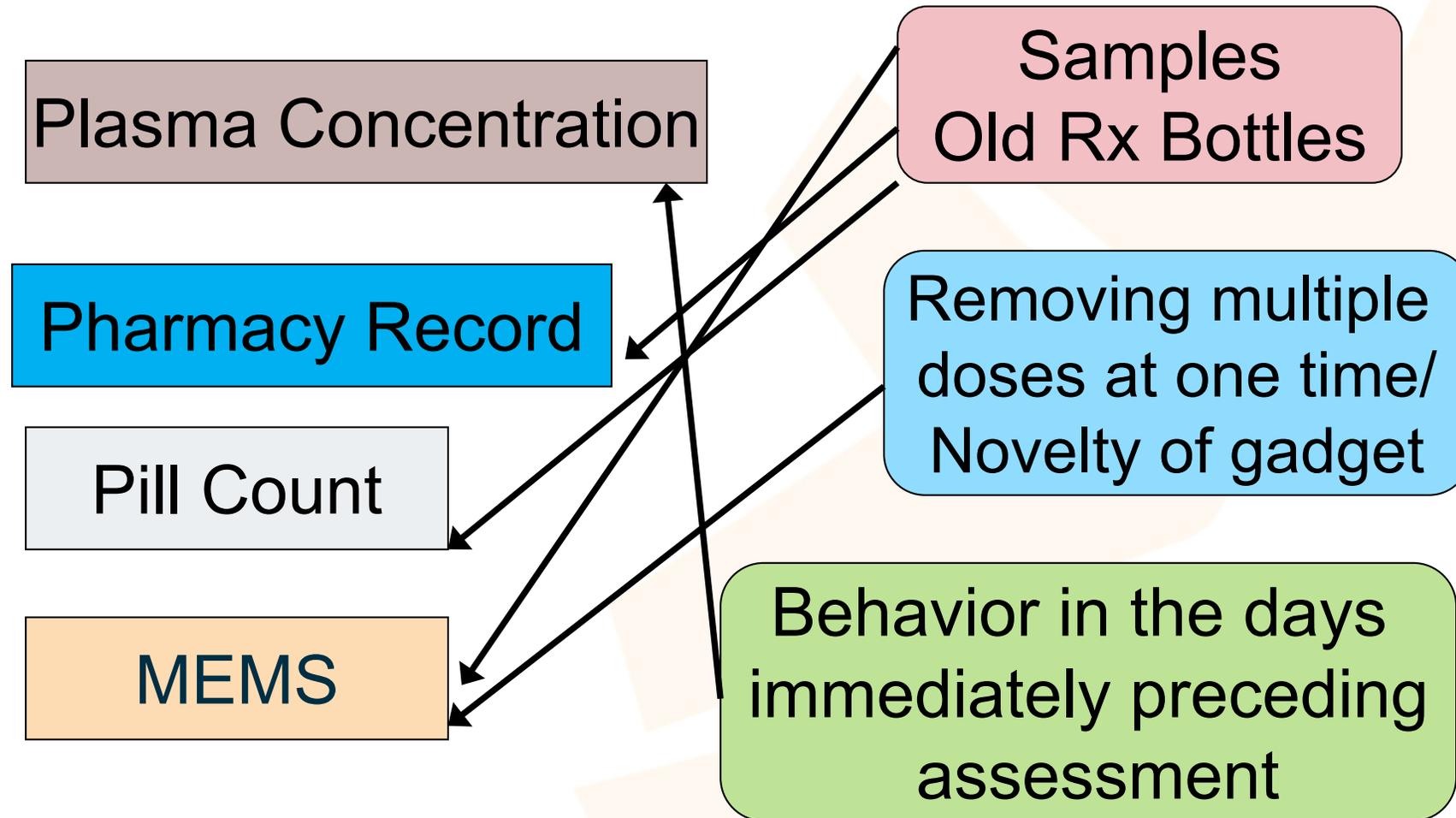


Has anything changed in the past decade?



Velligan D, et al. The assessment of adherence to oral antipsychotic medications: What has changed in the past decade? *Schizophr Bull.* 2019;45(Suppl 2):S351-S352. Velligan D, et al. *Schizophr Res.* Under review.

Old School Measures and Sources of Error



MEMS = medication event monitoring system.

Velligan DI, et al. *Schizophr Bull.* 2006;32(4):724-742. Levin JB, et al. *Ther Adv Psychopharmacol.* 2015;5(2):76-87. Velligan D, et al. The assessment of adherence to oral antipsychotic medications: What has changed in the past decade? *Schizophr Bull.* 2019;45(Suppl 2):S351-S352. Velligan D, et al. *Schizophr Res.* Under review.

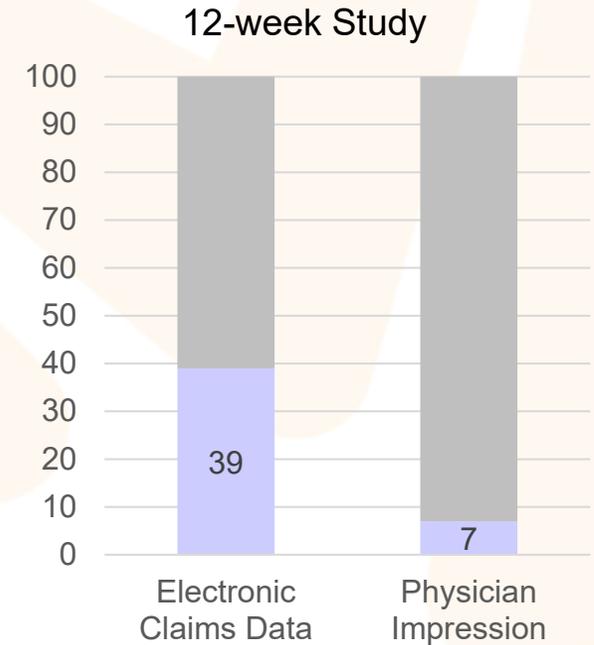
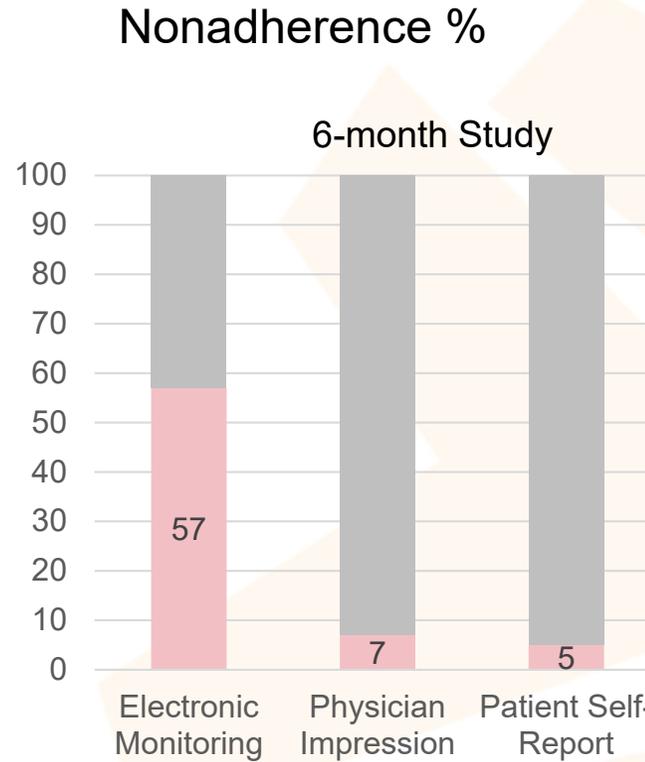
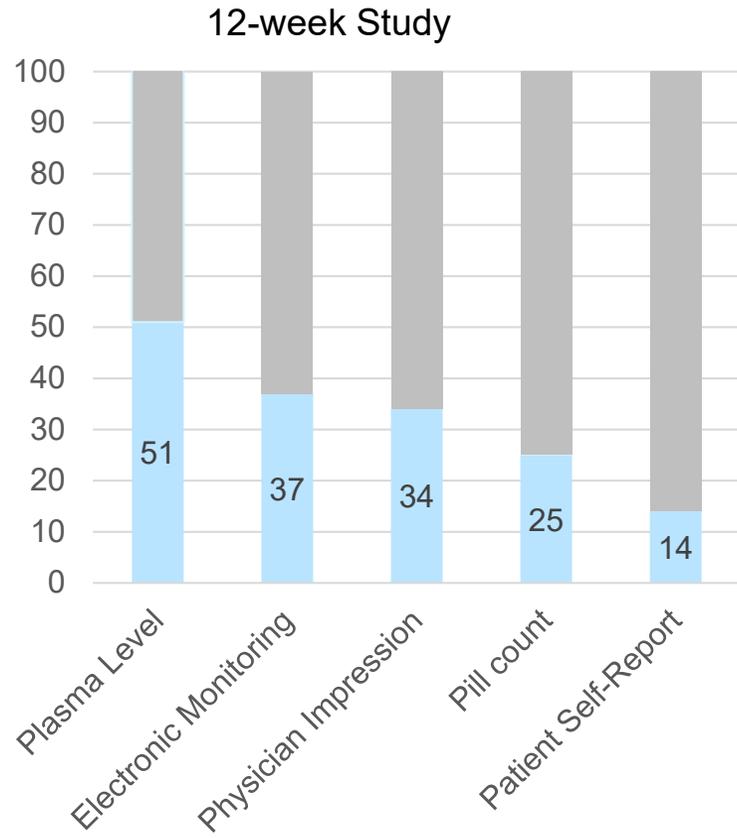
Can we really tell how much medication is being taken?

- Correlations between electronic MEMS and physician impressions of adherence are non-significant or minimal
- Using a standard 80% cutoff, physicians were unable to dichotomize patients into adherent and nonadherent groups



now it feels
LIKE WE'RE
guessing

Can we really tell how much medication is being taken?



Risks of Misidentifying Problem Adherence in Clinical Practice

- Changes or additions to medication regimen in an effort to “treat” nonadherence
 - Represent an inefficient use of resources
 - Can obscure accurate determination of medication response
 - Are unlikely to improve clinical state
 - Put the individual at increased risk of toxicity and medication adverse effects



How is adherence assessed in clinical practice?

- Practically speaking, we ask people
- How you ask is important
- What you ask is important
- It has to be OK to tell you that medication has not been taken as prescribed or don't bother asking

- Normalize missed medication,

“Many people forget to take their medication at times. Does that ever happen to you?”

- We can do better!!! Technology can help.



Use of Tablets in the Waiting Room

- Can help in assessing medication adherence
- Can help in assessing factors that predict nonadherence such as side effects and lack of efficacy
- Information can automatically be transferred to the medical record



Assessing Side Effects: Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)

INSTRUCTIONS: Select the best response for the following three questions:

1. Choose the response that best describes the frequency (how often) of the side effects of the medication you have taken within the past week for your depression. Do not rate side effects if you believe they are due to treatments that you are taking for medical conditions other than depression. Rate the frequency of these side effects for the past week.

No side effects	Present 10% of the time	Present 25% of the time	Present 50% of the time	Present 75% of the time	Present 90% of the time	Present all the time
<input type="checkbox"/>						
0	1	2	3	4	5	6

2. Choose the response that best describes the intensity (how severe) of the side effects that you believe are due to the medication you have taken within the past week for your depression. Rate the intensity of the side effect(s), when they occurred, over the past week.

No side effects	Trivial	Mild	Moderate	Marked	Severe	Intolerable
<input type="checkbox"/>						
0	1	2	3	4	5	6

3. Choose the response that best describes the degree to which antidepressant medication side effects that you have had over the last week have interfered with your day to day functions.

No impairment	Minimal Impairment	Mild Impairment	Moderate Impairment	Marked Impairment	Severe Impairment	Unable to function due to side effects
<input type="checkbox"/>						
0	1	2	3	4	5	6

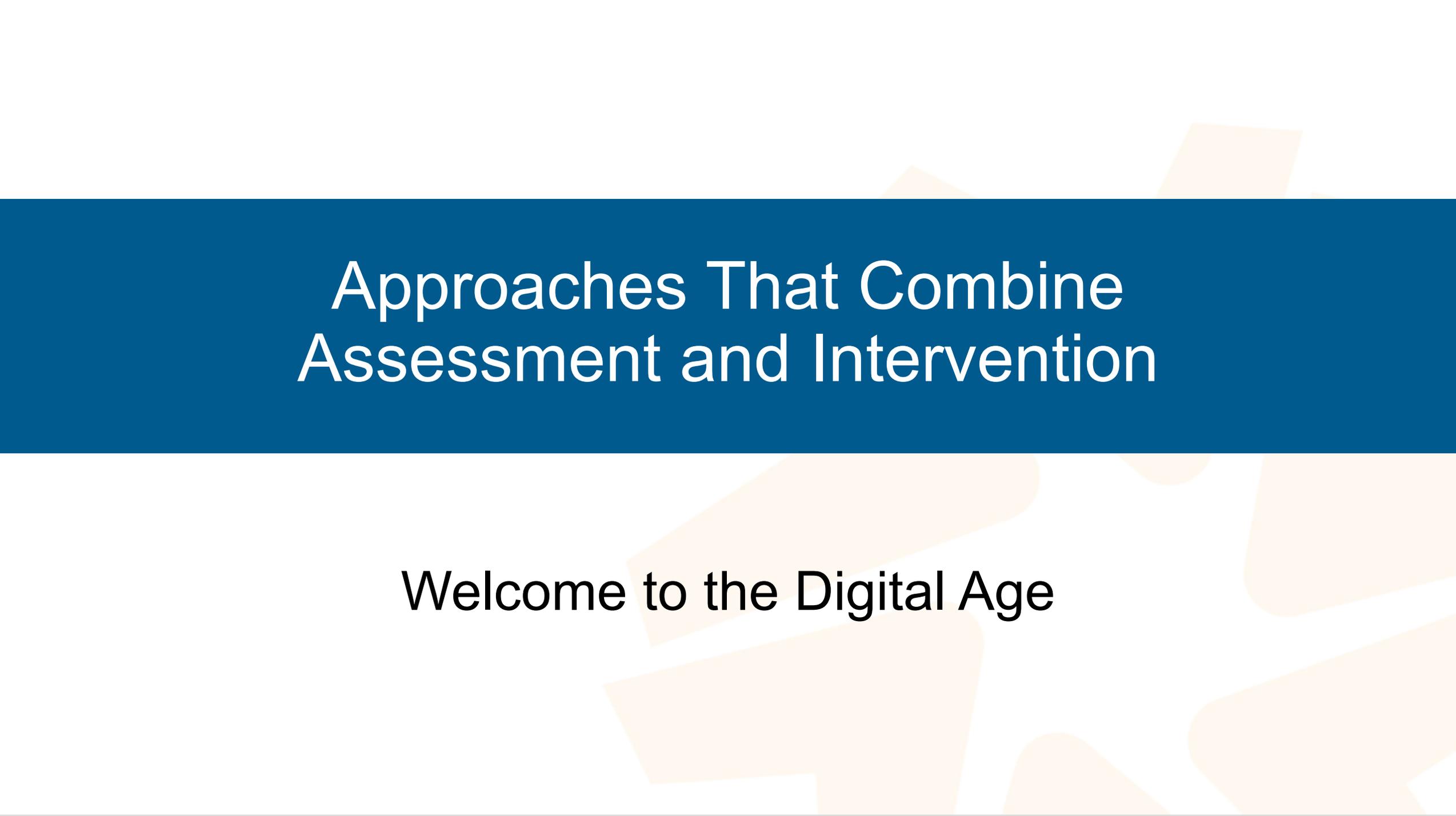
Simple Questions about Taking Medication

1. Taking medication as prescribed fits in very easily with my daily routine. Yes No
2. People often have to remind me to take my tablets. Yes No
3. It is easy to remember to take medication at the right time. Yes No
4. If my daily routine changes I have difficulty remembering to take my tablets. Yes No

Use of Tablets for Assessment in the Waiting Room

- Tablets are not intuitive
 - Individuals must be trained on use
 - Place in a location and use in a way that fits with existing workflow
 - Make surveys available in multiple languages
 - Icons rather than numbers help with lower literacy
 - Get staff buy-in





Approaches That Combine Assessment and Intervention

Welcome to the Digital Age

What works to improve adherence?

- Decrease drug dosing frequency and complexity
- Build in “cues” and automatic reminders
- Mobilize environmental supports when available (automatic refills, helpful family involvement)
- Identify and target patient-level barriers and facilitators
- **Technology can facilitate patient-provider communication and increase support, but it is not in itself the solution !**

Digital Age Assessment/Intervention Hybrids

- EMR prompts to promote adherence assessment
- Smartphones – texting, ecological momentary assessment, commercially available apps
- Integrated data platforms that communicate with the medical record, eg, Tablet Assessment
- Really smart pill containers
- Really smart pills
- Electronic reminders for prompting prescribers in the medical record specifically designed to improve adherence in mental health

Medical Records Pop-ups to Improve the Identification of Those with Suboptimal Outcomes

Individuals **Not** receiving **Optimum** Benefit from antipsychotic medication (**NOB**) Checklist:

1. Based upon the patient's report, caregiver report, or your prescribing record, the patient has missed doses	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2. Patient is currently on more than 1 antipsychotic (not during a switch)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3. Patient has been on more than 2 antipsychotics in the past 12 months	<input type="checkbox"/> Yes	<input type="checkbox"/> No
4. Patient has been hospitalized or had a crisis visit in the past 12 months	<input type="checkbox"/> Yes	<input type="checkbox"/> No
5. Patient is not satisfied with current level of symptom control	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Any **YES** answer should alert you that **LAI** may help you in clinical decision-making and improve outcome for your patient!!

I offered LAI to this patient	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> N/A
Patient accepted LAI	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> N/A

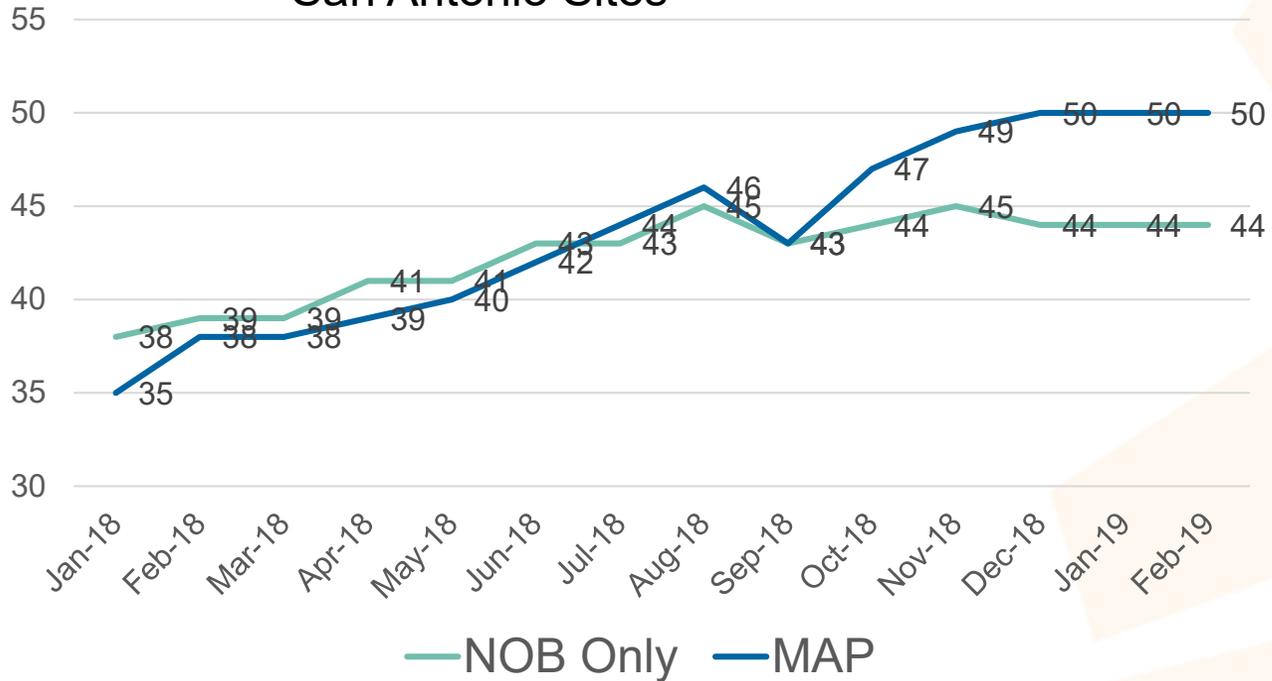
Velligan and Sajatovic 2012

Rather than identify who is and is not adherent, the NOB helps identify those who may benefit from a change to Long-Acting injection. This allows the treatment team to know as soon as doses are missed so that intervention can occur.

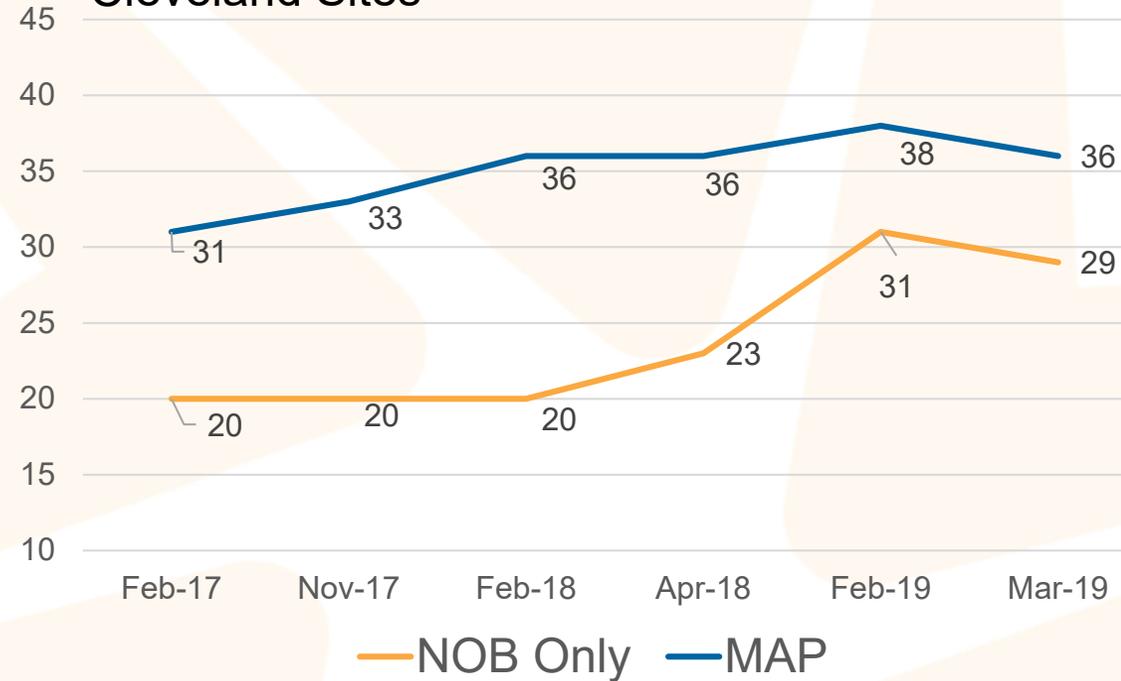


Keeping Adherence in Mind

San Antonio Sites



Cleveland Sites



Smartphones: Simple, Inexpensive Texting

- Input person's cell number
- Input time(s) of day medication is taken (customized to person's schedule)

It's 8 AM, time to take your medication

Smartphones: Simple, Inexpensive Texting

- Did you take it?
- Respond Yes or No

Smartphones: Simple, Inexpensive Texting

- Good job
or
- Would you like another
reminder in an hour?

Text Messaging Assessment and Intervention

- Yes
- Forgot
- Did not want to

Great work.
Medication helps
you stay on track!



- Yes
- Forgot
- Did not want to

Good plan. An
alarm will remind
you every day!

Have you taken
your medication
today?

- How can you
remember?
- Post it on
mirror
 - Pill box
 - Alarm
 - Support person
 - Other

Try setting an
alarm and see if it
helps you in the
next few days

Text Message Reminders and Efficacy

- A meta-analysis of 16 RCTs using text reminders—provided evidence for the short-term effectiveness of text messaging reminders
- 2742 patients; multiple chronic diseases
- Adherence almost doubled, clients thought it was helpful and were satisfied
- Those with multiple reminders daily at inconvenient times (one study) found it intrusive and inconvenient. Speaks to need to customize around patient schedules
- Short-term over 6 months. Less evidence for long-term—are you building habits?



RCT = randomized controlled trial.

Thakkar J, et al. *JAMA Intern Med.* 2016;176(3):340-349.

Caveats

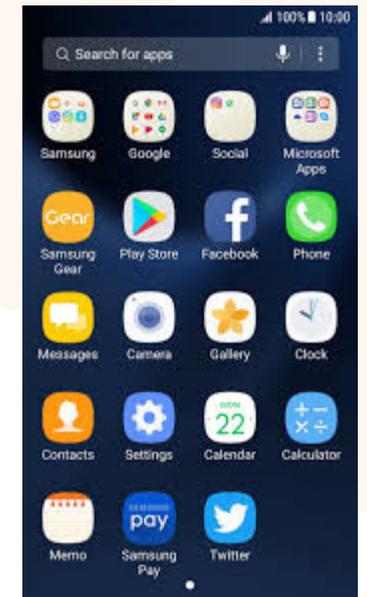
- Timely risk management can be an issue
- If patients are texting messages about concerns with treatment—*Does this open providers up to liability?*
- If patients don't delete text messages—or there is not an automatic delete feature—*Are these retrievable?*
- The legal issues have not really caught up with available technologies

Commercially Available Smartphone Apps

- Identified 160 smartphone apps for medication adherence
- Ranked on a number of measures of functionality and usability
 - Free
 - Online data entry only
 - Tracking missed and taken doses
 - Database of medications
 - Complex instructions
 - Sync and export, cloud functions
 - Generates reminders with no connectivity
 - Multiple platforms (iPhone, Android); multiple languages
 - Able to print data for provider

Smartphone App Features

- The **ability to track missed doses and provide print out for provider available in only 30% of apps**
- 10 apps with highest number of desirable features subjected to testing
 - Most intuitive, easy to use, met claims of developer, and provided satisfactory reminders
 - MyMedSchedule, MyMeds, and RxmindMe given highest ratings



Do smart apps help?

- Use is based upon motivation of the user to a great extent
- A Cochrane review of RCTs indicate that only half demonstrated improvements in long-term adherence and outcomes
- Best apps were embedded in a complex treatment strategy to improve adherence
- Conclusion: Apps can be a component of multi-modal strategies to improve long-term adherence and outcomes
- However, that review was done in 2008 and it is possible that technology is more user friendly and better and maybe more tolerable for long-term use

What about simpler use of smartphones?



- Google Hangouts, Apple FaceTime for direct observation of medication taking?
- *HIPAA compliant?* No real consensus
- *Are phone calls any less HIPAA compliant?*

What about simpler use of smartphones?

- Business Associate Agreement (BAA) is necessary if a vendor creates, receives, maintains, or transmits PHI on behalf of a HIPAA-covered entity or one of its business associates. Needed for cloud services. Telemedicine platforms fall into this category
- Grey area: VA and other government entities see Apple FaceTime, Google Hangouts etc. as allowable because these are viewed as conduits. No BAA is needed for a conduit. Conduits are “transmission only” services, no data storage
- No technology can be HIPAA compliant only a user can be
- Better guidance is needed before compliance offices will be comfortable



PHI = protected health information.

Haynes RB, et al. *Cochrane Database Syst Rev.* 2008;(2):CD000011. www.hhs.gov/hipaa/for-professionals/faq/2077/can-a-csp-be-considered-to-be-a-conduit-like-the-postal-service-and-therefore-not-a-business%20associate-that-must-comply-with-the-hipaa-rules/index.html. Accessed July 8, 2019.

Facial and Pill Recognition in a Smartphone

- Recognizes the person placing pill on tongue, swallowing, and with empty mouth
- Computes deviations and identifies behaviors that may indicate non-ingestion



Really Smart Pill Containers



Features of Smart Pill Boxes

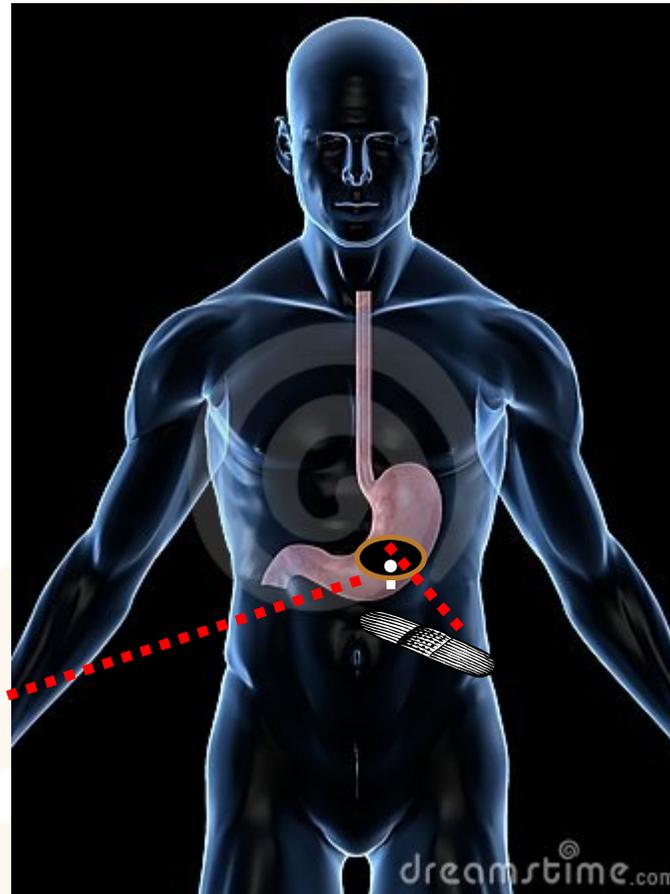


- Prompt the taking of medication
- May be able to list or speak the medication name and reasons for taking it
- May include cameras to see which pills are removed from the container
- Automatic download of information to secure server through phone line or Internet
- Some can provide positive feedback or deliver other messages
- Caveats
 - Opening and ingestion are not the same
 - Must be correctly filled, this can be a challenge
 - Use might need to be trained

Evidence

- Large studies in internal medicine showed no difference in adherence
- Randomized trial in schizophrenia with patients willing to take medication showed that compared to standard care, electronic pill containers led to improved adherence (~ 60% and 80% adherence, respectively)
- Often requires in home or pharmacy fills
- Setting container where medications are taken and device can be heard
- Willingness to take medication

Even Smarter Pills: Drug-Device Interface



Drug–Device Interface

- When ingested and contacts stomach, the sensor sends a signal to a patch worn by the patient and this transmits data to any Bluetooth® enabled device to give information to the patient, caregivers, or providers with the consent of the patient
- Allows providers to treat more patients than if Directly Observed Therapy (DOT) is needed
- Has been used in tuberculosis, hypertension, and schizophrenia

Drug–Device Interface

- What is the evidence?
 - People were able to follow the necessary procedures; acceptability even in schizophrenia
 - In hypertension, 95 patients who had failed 2 medications and metformin were enrolled in a 12-week program using the interface or to standard care
 - Results included lower systolic and diastolic blood pressure, and lower levels of low-density lipoproteins in interface group compared to standard care
 - Much more work to be done

Drug–Device Interface

- Caveats?
 - Data sharing and privacy issues as information is transmitted via Bluetooth[®] device
 - Consent of the patient regarding sharing data with the provider is imperative

Conclusions

- Use of technology as a component of adherence promotion is evolving rapidly, although there are still many unanswered questions
- Technology-assisted methods are a communication platform, not a substitute for good clinical care. Establishing a strong therapeutic relationship between patients and clinicians is essential to optimizing adherence
- Technology introduces privacy issues and multiple caveats
- There is no perfect method of assessing adherence, but more direct and objective measures are becoming available
- Selection and application of technology should be driven by a careful assessment of patient-level barriers and facilitators to adherence
- Adherence evaluation and promotion is a continuous process