

Leveraging Existing Resources to Improve Medication Information

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AAFP National Research Network

- A successful practice-based research network
- 1300+ clinicians in 48 states within our primary network and 14 affiliated regional network
- Basic research infrastructure in place
- 15 core staff with 6 times that many staff in the affiliated networks

Why?

- **Networks (can) capture events that reflect the selection and observer bias that characterize primary care in community-based patient populations.**
- **(Networks) can provide access to the practice experience and care provided by full-time primary care clinicians.**
- **(Networks) can focus their activities on practice-relevant research questions.**

Nutting PA, Beasley JW, Werner, JJ. Practice-Based Research Networks Answer Primary Care Questions. *JAMA*, 1999;281:686-688.

Mission of AAFP NRN

To conduct, support, and promote
research in practice-based settings

The Electronic Present

- Family physicians lead the way in the use of electronic health records (30+%)
- AAFP has been a leader in data interoperability between EHRs
- AAFP NRN establishing an electronic sub-network with data connectors in place that standardize data extraction across multiple platforms

ePCRn

- "The electronic Primary Care Research Network (ePCRn) is a sophisticated electronic architecture that facilitates practice-based research in primary care clinical practices throughout the country. Through the Federation of Practice-Based Research Networks (FPBRN), the ePCRn provides new research tools to enhance health care delivery in community practices."

NIH Roadmap Initiative "re-engineering the clinical research enterprise"

- Can manage information at the practice and patient level for research and quality improvement purposes
- Identify potential study subjects using the full EHR data set
- Track patients over time
- Guide research protocols at the time of visits

Multi-Use System

- Network infrastructure exists for wide variety of activities
- Network and its affiliates have track record
- Adding medication related data collection expands uses and funding opportunities
- Improving knowledge of medication safety and effectiveness will benefit clinicians and patients

**N-of-1 Tests in Primary Care:
A New and Better Way to
Prospectively Monitor
Chronic Care Drugs for Safety**

AAFP/Opt-e-scrip, Inc.

Introduction

- Evidence-based medicine experts consider N-of-1 drug investigations to be the highest evidence for making individual patient drug treatment decisions
- The aggregated use of a series of N-of-1 studies generates a continuously expanding database of prospectively documented effectiveness and safety outcomes in support of age, sex, ethnic, and drug interaction subgroup risk/benefit assessments resulting in safer prescribing

What are N-of-1 Tests?

- ❖ Single-patient, double-blind, randomized, repeated-crossover investigations to measure risk/benefit for a newly **marketed drug vs. placebo**, or to measure relative effectiveness and safety **for two marketed drugs** for **labeled indications and doses** in a single prescription
- ❖ Standardized and validated for ease of use by practicing physicians and for data aggregation
- ❖ Powerful

Power

- Events are crossover intervals, not # of patients
- 4 crossovers typically provides the ability to detect a 20% difference with 80% power.
 - N of 1 trials are quick and inexpensive.
- Aggregating N of 1 trials results in an order of magnitude difference in the number of patients required to maintain the same power as a parallel groups design.

The AAFP/Opt-e-scrip Solution

- Test newly approved drugs in a highly sensitive, repeated-crossover, placebo-controlled design. Re-test among responders periodically for longitudinal effects.
- Aggregate the individual data and stratify by sub-group to determine more appropriate sub-groups for re-prescribing and to determine risk levels by sub-group
- **The result: A safer prescribing environment created by identifying both known and unknown adverse events among population sub-groups**

How Does the American Medical Association Assess N-of-1 Data?



AMA Working Group on EBM recommends physicians seek strongest evidence for treatment decisions: “N-of-1” randomized trial; AMA has assigned CPT Code 0130T

THE MEDICAL LITERATURE

Users' Guides to the Medical Literature XXV. Evidence-Based Medicine: Principles for Applying the Users' Guides to Patient Care

Gordon H. Guyatt, MD, MSc
R. Brian Haynes, MD, PhD
Roman Z. Jaeschke, MD, MSc
Deborah J. Cook, MD, MSc
Lee Green, MD, MPH
C. David Naylor, MD, PhD
Mark C. Wilson, MD, MPH
W. Scott Richardson, MD
for the Evidence-Based Medicine Working Group

This series provides clinicians with strategies and tools to more effectively integrate evidence from published research in their care of patients. The 2 key principles for applying all the articles in this series to patient care are:

Table 1. A Hierarchy of Strength of Evidence for Treatment Decisions

N of 1 randomized trial
Systematic reviews of randomized trials
Single randomized trial
Systematic review of observational studies addressing patient-important outcomes
Single observational study addressing patient-important outcomes
Physiologic studies
Unsystematic clinical observations

CLINICAL SCENARIO
A senior resident, a junior attending, and an emeritus professor were discussing evidence-based medicine (EBM) over lunch in a hospital cafeteria.
"EBM," announced the resident with some passion, "is a revolutionary development in medical practice." She went on to describe EBM's fundamental innovations in solving patient problems.
"A compelling exposition," marked the emeritus professor.
"Wait a minute," the junior resident exclaimed, also with some passion, "presented an alternative position that EBM merely provided additional tools for traditional approaches to patient care."
"You make a strong and convincing case," the emeritus professor commented.
"Wait a minute," the senior resident exclaimed to her older colleague.
See also Patient Page.

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Currently Available N-of-1 Test



Example of a Study Design: Allergic Rhinitis N-of-1 Investigation

STUDY DAY							
1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32
Crossover Pair 1		Crossover Pair 2		Crossover Pair 3		Crossover Pair 4	

- Days 1 to 4 Patient takes Treatment A
- Days 5 to 8 Patient takes Treatment B
- Days 9 to 12 Patient takes Treatment B
- Days 13 to 16 Patient takes Treatment A
- Days 17 to 20 Patient takes Treatment B
- Days 21 to 24 Patient takes Treatment A
- Days 25 to 28 Patient takes Treatment A
- Days 29 to 32 Patient takes Treatment B



Opt-e-scrip™



INSTRUCTIONS

1. You will take 2 doses of medicine daily.
2. Take your first dose the morning following the day that the test kit is received (not the same day). The morning dose must be taken at breakfast time and the evening dose approximately 12 hours later.
3. It is very important that you take the medication (morning and evening) in the exact order printed on the blister package. You must use the medication labeled Day 1 first. Take the dose labeled AM in the morning and take the dose labeled PM in the evening. The next day you will take the medication labeled Day 2, and so forth.
4. If you miss a dose on a particular day, skip the missed dose and take the next appropriate dose at the scheduled time.
5. Discard any unused medication.
6. Do not take any other allergy, sinus or cough/cold medication (prescribed or over-the-counter) to treat your allergy symptoms; do not change the way you use other chronic medications during the 32 days of this test, unless otherwise directed by your doctor.
7. In addition to taking test medication, you need to tell us: (a) how the product affects your allergy symptoms; (b) its side effects; (c) and any medication that you have taken in addition to the test medication. See General Instructions Card on how to send us your information.
8. We have included an additional 12 days of medication for dosing during the interim period after you have sent us all of your information and before your next prescription is written.
9. For Pharmacy assistance, call 1-866-678-3727 or email us at pharmacist@opt-e-scrip.com.

ALLERGIC RHINITIS Blister pack

Contains 4 days of medication

AM

PM



DAY
1



DAY
2



DAY
3



DAY
4

**Blister Card
with
Instructions**

Daily Diaries for Quick Recording of Effectiveness and Side Effects

Patient 01 - 001853 Diary for Blister Card 2 **DO NOT FOLD**

CAUTION: This package NOT CHILD RESISTANT. Store this and all medications out of reach of children.

Please rate each symptom below:	DAY 1				DAY 2				DAY 3				DAY 4				OVERALL RATING DAY 4
	absent	mild	moderate	severe													
Sneezing	<input type="radio"/>	Please indicate the number of the diary page you have finished the mean of the diary since you have finished the mean of the diary in this blister card. How would you rate this drug for relief of your allergy symptoms? <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> 8 <input type="radio"/> 9 <input type="radio"/> 10 <input type="radio"/> 11 <input type="radio"/> 12 <input type="radio"/> 13 <input type="radio"/> 14 <input type="radio"/> 15 <input type="radio"/> 16 <input type="radio"/> 17 <input type="radio"/> 18 <input type="radio"/> 19 <input type="radio"/> 20															
Runny Nose	<input type="radio"/>																
Stuffy Nose	<input type="radio"/>																
Itchy Nose	<input type="radio"/>																
Tearful Eyes	<input type="radio"/>																
Itchy Eyes	<input type="radio"/>																

PLEASE DON'T FORGET TO RECORD ANY SIDE EFFECTS OR ADVERSE EVENTS ON THE OTHER SIDE OF THIS CARD.

Allergic Rhinitis Diary FORM 6 Opt-e-dip

CAUTION: Federal or state law prohibits transfer of this drug to any person other than patient for whom prescribed.

Diary for Blister Card 3 **DO NOT FOLD**

Did you experience any of these Side Effects or Adverse Events?	DAY 1				DAY 2				DAY 3				DAY 4			
	Absent	Mild	Moderate	Severe												
Headache	<input type="radio"/>															
Sleepiness	<input type="radio"/>															
Fatigue	<input type="radio"/>															
Dry Mouth	<input type="radio"/>															

Notes: If you used another drug to treat a Side Effect or Adverse Event, please include this drug on your Additional Medication(s) Record.
 If you had a Side Effect or Adverse Event not shown above, please note this on your Additional Side Effect(s) Record.

Allergic Rhinitis Diary CONTINUED ON OPPOSITE SIDE. FORM 5 Opt-e-dip

CAUTION: This package NOT CHILD RESISTANT. Store this and all medications out of reach of children.

For urgent pharmacy assistance please call 1-866-678-3727.

	DAY 1	DAY 2	DAY 3	DAY 4
AM	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
PM	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

CAUTION: Federal or state law prohibits transfer of this drug to any person other than patient for whom prescribed.

Single Patient Drug Trial Comparing Two Acid Suppression Agents for Maintenance of Healing of Erosive Esophagitis - GERD

Nature of Single-Patient Drug Trial

This was a double-blinded, randomized, 3 paired-period multiple-crossover study comparing Omeprazole 20 mg qd to Ranitidine 150 mg bid each taken for 14 days at a time. Significance is shown for the single patient test when population data feedback is applied. The purpose of the test was to generate data on the comparative effectiveness and adverse event profile of these two test conditions to guide future treatment.

Findings & Conclusions

Effectiveness

Omeprazole was significantly superior to Ranitidine in *Heartburn*.
Omeprazole was significantly superior to Ranitidine in *Regurgitation*.
Omeprazole was significantly superior to Ranitidine in *Rescue Medications*.
Omeprazole was significantly superior to Ranitidine in *Patient Global Score*.

Adverse Events

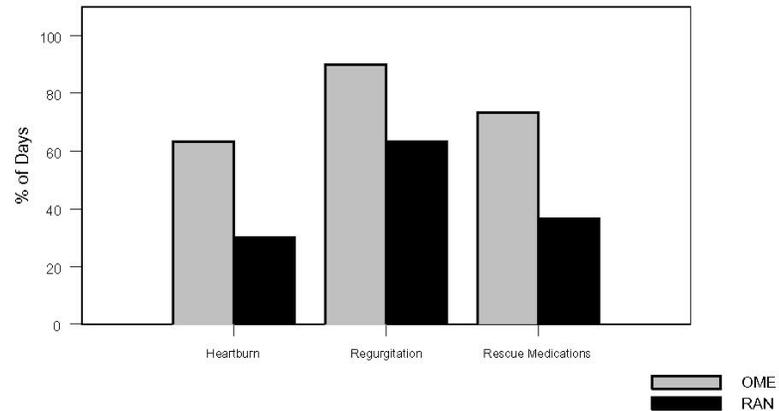
No significant treatment difference in *Headache*.
No significant treatment difference in *Rash*.
No significant treatment difference in *Diarrrhea*.
Omeprazole had significantly lower incidence than Ranitidine in *Lower Stomach Pain*.
Omeprazole had significantly lower incidence than Ranitidine in *Nausea*.
No significant treatment difference in *Vomiting*.
No significant treatment difference in *Constipation*.
No significant treatment difference in *Bloating*.
Omeprazole had significantly lower incidence than Ranitidine in *Excess Gas*.

Guidance

Omeprazole appears to be an appropriate treatment for this patient.

Treatment Key: OME = Omeprazole RAN = Ranitidine

Physician
Report
with
Guidance

1. PERCENTAGE OF SYMPTOM & RESCUE-FREE DAYS¹

Treatment Comparisons

	OME	RAN	
Heartburn	63.3%	30.0%	P = 0.010 * (statistically significant)
Regurgitation	90.0%	63.3%	P = 0.015 * (statistically significant)
Rescue Medications	73.3%	36.7%	P = 0.004 * (statistically significant)

Note: Number of Days Analyzed: 30 for OME; 30 for RAN.

1. For Days 5-14 in treatment period. Days 1-4 excluded due to possible carryover effects

Treatment Key: OME = Omeprazole RAN = Ranitidine

Detailed
Information
on
Effectiveness

We Propose: The AAFP NRN using Opt-e scrip N of 1 Methodology

- AAFP's research network is practice-based with over 1300+ clinician members in 48 states.
- Virtually any age/sex/ethnic/other sub-group could be enrolled in a given investigation of a newly approved drug
- N-of-1 data capture augmented through CINA with data connectors to thousands of physicians EMR systems and ePCRN which is already in place

Proposed Phase IV Process

- Protocol for N-of-1 validated
- IRB approvals obtained
- Physician network trained
- SOP's for assembling N-of-1 tests established at cooperating mail order pharmacy
- Tests dispensed pursuant to a valid prescription
- Individual patient data collected, analyzed, reported, then aggregated, and re-analyzed by subgroup
- Tests periodically re-prescribed to responders for longitudinal assessment; data re-aggregated

Can N-of-1 Tests Make Proactive Monitoring a Reality?

- ❖ Tests are easy to implement
- ❖ Tests are patient friendly and generate a usable database quickly
- ❖ Efficacy and side effect data from tests can be combined with objective physiological markers vastly strengthening the patient diary portion of a design
- ❖ Tests eliminate between patient error and patient by treatment interaction error

Are N-of-1 Tests Cost Effective?

- ❖ Tests are inexpensive; typically \$300-500 per patient
- ❖ Up-front costs involving validation, IRB approvals, and network training same as any trial
- ❖ Substantially greater data collection without additional physician participation
- ❖ Standard analysis for each patient for any given comparison

Benefits to Patients

- ❖ Most importantly, each patient personally benefits evidence based prescribing.
- ❖ Pre-screening efficacy and tolerability results in better relief with fewer side effects
- ❖ Non-responders identified quickly
- ❖ Better compliance and persistence as patient has is personally involved in drug selection process

What is Patient Persistence with the Current Tests?

- ❖ 98% for Allergic Rhinitis
- ❖ 88% for GERD
- ❖ 86% for Osteoarthritis

Overall Rate¹ was 90%

Note: Studies from the literature document that 25-50% of patients discontinue chronic care drug therapy after just 30 days.

1. Percentage of enrolled patients providing sufficient data for a therapeutic decision to be made.

Summary

- ❖ AAFP is currently involved in a Standard of Care trial and thus has N-of-1 experience. New collaborative trials have been written and are being fielded.
- ❖ N-of-1 tests are the highest form of evidence for making individual drug treatment decisions
- ❖ They yield statistically valid data and are recognized by the AMA
- ❖ Patients benefit directly
- ❖ N-of-1 test data, once aggregated, could be a highly sensitive Phase IV surveillance system
- ❖ N-of-1 Tests are relatively inexpensive to use in a primary care setting
- ❖ N-of-1 tests are already commercially available

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