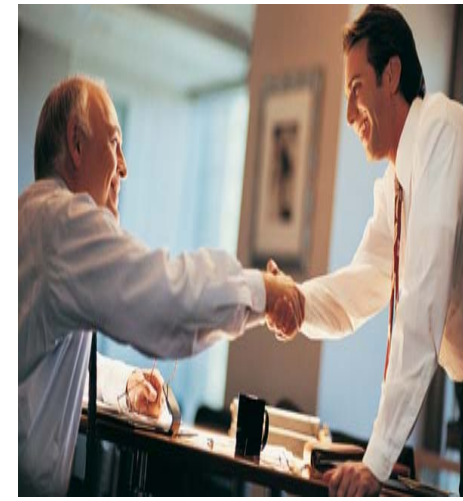
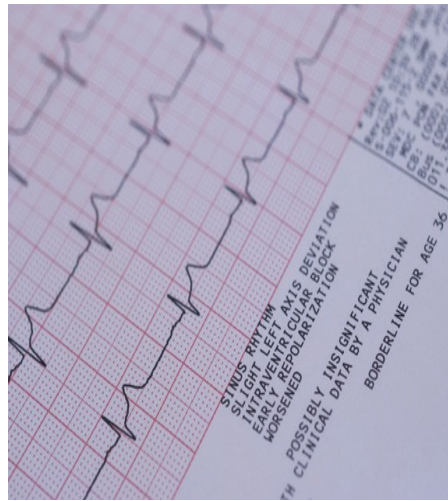


Selecting Surveillance Mechanisms for Opioid Products

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Edgar H. Adams, Sc.D.
Executive Director, Epidemiology
Covance



Objectives

- Goals of a RiskMAP for the Intended Population
- Goals of a RiskMAP for the Unintended Population
- Choosing Risk Management Strategies in the Population for Whom the Drug is not Intended (inadvertent exposure and addict populations).

Goals of an Opioid Risk Management Program for the Intended Population

- To ensure that patients obtain the benefits of analgesia while minimizing the risk to the patient
- To encourage appropriate prescribing (proper patient selection)
- To ensure that opioids are available to patients
- To minimize inadvertent exposure

Risk Minimization Action Plans for Patient (Intended) Populations

- **Appropriate Professional Labeling**
 - Black Box Warning
- **Targeted Education and Outreach**
 - Health Care Practitioner Letters
 - Training Programs
 - Focused or limited promotional techniques
 - Continuing education for healthcare practitioners
 - Patient labeling
- **Reminder Systems**
 - Patient agreement or acknowledgement forms
 - Certification programs for practitioners (Subutex/Suboxone)
 - Special product packaging (Actiq)
- **Performance Linked Access Systems**
 - Prescription only by certified health practitioners (Subutex/Suboxone)

Goals of an Opioid Risk Management Program for the Unintended Population

- To minimize diversion from the supply chain (RFID)
- To minimize access by the addict (PMP, Tamper Proof Pads)
- To monitor diversion through post marketing surveillance
- To reduce abuse and the complications of abuse

What Impact Does This Belief Have on RiskMAPS

- Opioids have important benefits in alleviating pain but are associated with **significant risk of overdose, abuse, and addiction**

Source: FDA Guidance Development of Risk Minimization Action Plans (RiskMAP)

Risk Minimization Action Plans for Street (Unintended) Populations

■ Key Attributes

- Population selected should be likely to abuse sufficiently early to identify emerging problem.
- Data must be timely so that an emerging problem will be identified quickly.
- Geographic coverage should be sufficiently broad that patterns of spread and persistence will be identified.
- Product Specific data available

- Where possible data should be presented as RATES

Approaches to Date

Independent Steering Committee

Expert Advisory Board

Analysis of Federal Data

Key Informant Surveys

Diversion Surveys

Poison Control Centers

Add questions to Surveys

Impaired Health Professionals

Prospective Patient Surveys

Surveys of Treatment Facilities

Ethnographers

Field Research/Site Visits

Case Assessment

Liaison with Organizations (e.g. NASCSA, NADDI)

What are we measuring & Is it Timely?

APPROACH	RELEVANT POPULATION	MEASURE	TIMELY DATA	GEOGRAPHIC COVERAGE	SCIENTIFIC SAMPLE
NHSDUH	Household	Lifetime Prevalence	No	Nat'l & State	Yes
DAWN	ED & ME	Consequences	Yes/No	Nat'l & City	Yes
TEDS	TX Admissions	TX Admissions	No	Nat'l & State	No
NFLIS	Seized Drugs	Drug ID, No dosage units	No	Nat'l & Regn'l	No
Key Informant	Yes/selected	Abuse	Yes	Nat'l & Zip Code	No
Diversion	Police	Diversion Case	Yes	Nat'l & Zip Code	No
Poison Control	General Pop'l	Intentional & unintentional Exposure	Yes	Nat'l, St. & Zip	No
Impaired Prof.	Yes/early adopt	Exposure/persist	No	No	No
Pros. Pt. Study	Yes	Abuse/Depend	No	No	No
Ethnographer	Street Pop'l	Understanding	Yes	Yes/No	No
Field/Site Visit	Signal	Signal verification	Yes	Yes/No	No
MD Survey	Selected	Awareness	Yes	Yes/No	No
TX Surveys	Selected	Use/Abuse	Yes	Yes/No	No

Children or Adults?

APPROACH	POPULATION	MEASURE	AGE GROUPS
NHSDA/NHSDUH	Household	Lifetime Prevalence	12 and older
DAWN	ED & ME	Consequences	All ages
TEDS	TX Admissions	TX Admissions	Primarily adults
NFLIS	Seized Drugs	Drugs Identified	NA
Key Informant	Selected	Abuse	Primarily adults
Diversion	Police	Diversion Case	Primarily adults
Poison Control	General Pop'l	Intentional and unintentional Exposure	All ages
Impaired Prof.	Early adopters	Exposure/persist	NA
Pros. Pt. Study	Patients	Abuse/Dependence	Adults
Ethnographer	Street Pop'l	Understanding	NA
Field/Site Visit	Signal	Signal Verification	NA
MD Survey	Selected	Awareness/Compliance	NA
TX Surveys	Selected	Use/Abuse	Primarily Adults
School Surveys	Grades 7-12	Use	12-19

Questions to Consider

- What is/are the key risk(s)
- What population(s) is/are at risk
- What populations are likely to abuse early
- Are data available
 - For the population of interest
 - Are they timely
- Will special studies need to be implemented
- Is there a denominator available

Examples

- Tramadol (drug with low abuse potential)
- Actiq (Potent drug concern about inadvertent pediatric exposure)
- Hydromorphone (Concern about abuse in addict populations)
- Nicotine Patch (Concern about use as a “gateway” drug)
- Ionsys (In hospital use)

Tramadol

- Methadone Maintenance Patients: A population of experienced drug users unlikely to be interested in a drug like tramadol
- Impaired Health Professionals:
 - Highly vulnerable population with easy access
 - Early adopters of Pentazocine and Fentanyl
- Key Informants: Selected for vulnerable populations, data obtained quarterly
- Diversion Investigators: What drugs are being diverted?
- Patients with Chronic Pain: Answer question about patients becoming addicted

Tramadol

- DAWN: Consequences of abuse (New Measures)
 - DAWNLIVE provides timely unweighted data but no geographic data
- NFLIS: Seizures (now quarterly but no geographic data)
- TESS: Data from Poison Control Centers on intentional and unintentional exposures (timely, geographic data?)

Actiq

- DAWN: DAWNLIVE can address Inadvertent pediatric exposure
- TESS: Inadvertent pediatric exposure
- Physician Surveys
- Pharmacy Surveys

Hydromorphone

- Methadone Maintenance Patients: Drug has a history of street use, this might be a good population
- Limited Rollout

Nicotine Patch

- Concerns about use as a “Gateway drug” might suggest initiating school surveys
- Adding questions to existing surveys

Ionsys

- In Hospital Use: Concerns about Diversion
- Large amount of residual drug

Review and Evaluation of Current Systems

- Attempt to systematically evaluate various systems using 7 core criteria identified by 3 experts (EA,HC, NK)
- Core Criteria: Population Coverage, data quality, timeliness, sensitivity of signal detection, geographic specificity, acceptability to respondents and questionnaire quality)
- 4 additional criteria: Simplicity, flexibility, record time, and independence
- Systems evaluated: National Household Survey on Drug Use and Health, Drug Evaluation Network System, Monitoring the Future, Treatment Episode Data Set, Toxic Exposure Surveillance System, Drug Abuse Warning Network.

Review and Evaluation of Current Systems

SYSTEM	CONTAINS ALL CORE CRITERIA	% OF CORE AND ANCILLARY CRITERIA SCORED EXCELLENT OR GOOD
DAWN	No	36%
NHSDUH	No	45%
MTF	No	45%
TEDS	No	18%
TESS	No	36%
DENS	No	36%

Conclusions

- All systems have flaws, but fortunately they can still be useful for Surveillance.
- Be aware of the weaknesses as well as the strengths
- Select the systems carefully to meet your needs based on the risk and product characteristics.
- Use multiple measures where possible

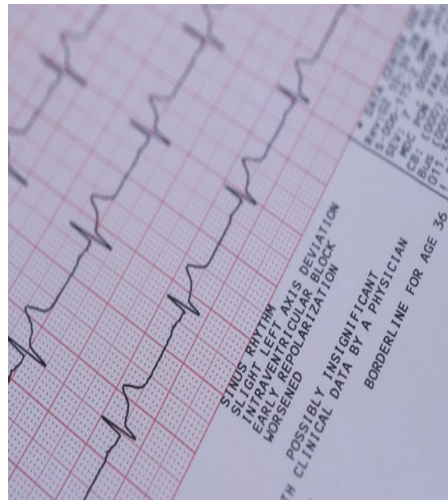
DISCUSSION

Toxic Exposure Surveillance System (TESS)

**Distribution of Intentional Tramadol exposures in TESS by Reason for Exposure
2004**

	Tramadol		Tramadol/APAP	
REASON	N	%	N	%
Abuse	240	11.1	63	8.4
Misuse	272	12.6	89	11.8
Suspected Suicide	1,524	70.6	550	73.1
Unknown	123	5.7	50	6.6
Total	2,159	100.0	752	99.9

Drug Abuse Warning Network (DAWN)



Comparison of Selected Characteristics for Tramadol Cases Classified as Overmedication or Other in DAWN July 1-December 31, 2003

	OVERMEDICATION	OVERMEDICATION	OTHER	OTHER
	N	%	N	%
N	44		34	
GENDER				
Male	14	32	13	38
Female	30	68	21	62
AGE				
0-20	7	16	4	12
21-34	13	30	15	44
35-44	12	27	7	21
45-54	8	18	5	15
55+	4	9	3	9
COM DIAGNOSES				
Drug Abuse Rel	26	59	28	82
AMS/Neurolog.	7	16	6	18
Sympt not Pain	4	9	5	15
None	7	16	0	

Percent Distribution of Combined Diagnoses for Selected Analgesics

July 1 – December 31, 2003b

	Paracetamol		Tramadol		Codeine		Propoxyphene	
	Ovrmd	Othr	Ovrmd	Othr	Ovrmd	Othr	Ovrmd	Othr
N	970	204	44	34	220	79	112	68
COMBINED DIAGNOSES	%	%	%	%	%	%	%	%
Drug Abuse Related	72	79	59	82	60	80	79	65
AMS/Neurological	22	7	16	18	7	8	12	12
Symptoms not pain	22	9	9	15	7	10	14	9
None	24	2	16	0	2	1	3	6

Benefit versus Risk

The difference between a drug and a poison is the
dose

(attributed to Paracelsus)

Basic Philosophy

- FDA Approval signifies that a product is safe and effective for its labeled indication and under its labeled conditions of use. This does not suggest the absence of risk
- Rather it suggests that the products benefits outweigh that potential harmful or undesirable effects.

Risk Management

- Premarket risk assessment + Post marketing pharmacovigilance = risk assessment
- Risk Minimization Action Plans (RiskMAPs)

When is a RiskMAP Needed?

■ Considerations

- Benefits compared to type, magnitude and frequency of risks
- Existence of Treatment Alternatives
- Population who benefits versus population at risk
- Preventability of adverse effects
- Will a RiskMAP encourage appropriate use

“FDA recommends that RiskMAPs be used judiciously to minimize risks without encumbering drug availability or other wise interfering with the delivery of product benefits to patients” “FDA RiskMAP Guidance”

Examples

- Opioids have important benefits in alleviating pain but are associated with significant risk of overdose, abuse, and addiction
- Some beneficial drugs may also be teratogenic

Source: FDA Guidance Development of Risk Minimization Action Plans (RiskMAP)