Risk MAPs

Best Practices in Opioid Risk Management

Tufts Health Care Institute Program on Opioid Risk Management

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Brief Background on Risk Management for Prescription Drugs

- Early Risk Management Plans (RMPs) preceded Risk Minimization Action Plans
  - Clozapine 1990
  - Thalidomide 1998
  - Actiq1998
- Managing the Risks from Medical Product Use
- FDA Risk Management Guidance Documents
  - PDUFA goal finalized in 2005

Guidance Contents

- Role of RiskMAPs
  - Assessment of Risks and benefits, minimization of risks and optimization of benefits
  - Strategic Safety program designed to meet specific goals and objectives in minimizing product risks
  - Uses one or more tools to meet desired health outcome
  - Goes beyond FDA-approved labeling

Examples of RiskMAP Goals and Objectives

Drug Products	Goal	Objective
Clozapine	No agranulocutosis	WBC monitoring
Thalidomide	No fetal exposure	Pregnancy monitoring and prevention
Dofetilide	Minimize torsades de pointes	Dose adjustment in renal impaired, hosptialize pts during initiation of therapy
Actiq	No pediatric deaths	No pediatric exposures

Tools

- *Labeling*
  - Cornerstone
  - May contain RiskMAP info in precautions or warnings
  - PPIs and Medication Guides
- *Communication tools*
  - Purpose to communicate risks and benefits of treatment based on the accumulated data generated on the product during development (culmination of NDA review)
  - Reinforces messages in RiskMAPs
  - Examples: videos/books/program guides/DHCP letters/CME
  - Target: public/patient/practitioner/pharmacist
  - Effectiveness unstudied/limited results (eg pregnancy protection for isotretinoin, LFT monitoring for troglitazone)

Tools (continued)

- Redundant reminders/prompting systems
  - Examples
    - Patient-MD agreements
    - Attestation
    - Pharmacy checking mechanisms (software/stickers)
    - Special packaging or limited supply of product
  - Provide additional communication opportunities/ rely on voluntary compliance

Tools (continued)

- Restricted distribution systems and Performance-linked access systems
  - Examples
    - SubPart H Approval
    - Mandatory registries or enrollment of patients, pharmacies, prescribers
    - Restrictions on prescriptions and refills, distribution and dispensing
  - Purpose:
    - Limits access to target population
    - Limits dispensing to authorized practitioners
    - Mandatory registration and enrollment provides mechanisms to measure plan effectiveness

RiskMAP evaluation

- Existing plans have very limited self-evaluation provisions
- Goal—ensure that resources expended on risk minimization are achieving the desired goals
- Tools:
  - Passive and active surveillance for events of interest/registries
  - Patterns of drug use/prescribing/population databases
  - Surveys to assess outcomes
  - Studies to assess knowledge and understanding of risk

Approved Opioids with RiskMAPs:

- Ultram
- **Actiq**
- Avinza
- OxyContin
- **Subutex/Suboxone**
- Palladone
- Duragesic,
- Opana
- Ionsys

Actiq (OT Fentanyl citrate)

- All features centered on key risks
- Key safety features
  - Accidental ingestion by children
  - Improper patient selection
  - Diversion or abuse
- Label –box warning and PPI
- Restricted distribution (Breakthrough Cancer Pain)
- No sales directly to retail pharmacy outlets
- Subpart H
- Units dispensed
  - Child resistant
  - Starter packs for titration
  - Price inversely proportional to dose

Actiq

- Communication/education
  - Welcome kit/redundant messages/patient videos and children's books tested for comprehension
  - CME, articles and professional monographs cleared by FDA prior to release—conveyed balanced message
  - Point of dispensing intervention (opioid naïve patients, children in home, welcome kit)
  - Focused detail education—label, PPI, safety video, 1-800 poison control number/disposal information/ product storage/ intervention (aggressive re-education) if off-label use >15% per quarter of sales for two consecutive quarters;
  - Follow-up phone call back system for comprehension and compliance check after initial prescription for first 1000 patients per retail pharmacy chain for during first year. Decision to continue or not pending results
  - Promotional message audit q 6 months

Actiq (cont)

Surveillance for Off-label use

- IMS
- Wholesaler data

Passive surveillance for adverse events

- AERs
- Literature monitoring
- TESS, DAWN, poison control data
- State control authorities/state boards for pharmacy

Actiq

- Provisions for rapid response to safety alerts

  Threshold: any pediatric exposure

  Question: was the program too restrictive?

Subutex (buprenorphine SL)

- Package insert: box warning, PPI
- Increased control to CIII
- Restricted distribution
  - DATA 2000/special training required for special DEA license
  - Limited to opioid addiction
  - Narrow distribution channel: Distribution point algorithm for assessing quantity of orders and suspicious orders/automatic reporting to DEA as they occur
  - Starter packs for initiation of treatment
- Mandatory education for prescribers

Subutex/Suboxone

- SARD (Substance Abuse Research Division) at Wayne State using multiple approaches to gather data
- Advisory Group
  - Ethnographers—street surveillance
  - Key informant networks
  - Club drug parties and Raves
  - Private practitioners
  - Media surveillance
- Passive Surveillance
  - DENS
  - DAWN
  - CEWG
  - others
- Active surveillance focus on diversion and abuse and will have milestones for evolution over 5 years

Five Ideals of Opioid RiskMAPs

- Clearly identified risks
- Program focused on most important risks
- Intervention appropriate to risk
- Balance of public safety and patient need
- Readjustments based on data-driven demonstrated success or failure