Managing Aberrant Drug-Related Behavior in Primary Care: A Systematic Review

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Clinical Context

• A primary care provider is considering prescribing a trial of chronic opioid therapy for a 56 year old male with post-laminectomy pain. What resources are there available to help this provider predict the likelihood of safe, successful treatment? How good is the evidence that has been used in developing these resources? How aware are primary care providers of these resources?
Introduction

• Increased opioid prescribing especially for the management of chronic noncancer pain has been accompanied by an increase in opioid abuse
• Primary care providers are not only concerned about the risk of opioid abuse- they are not necessarily confident regarding how to minimize the risk of such-they are also concerned about aberrant behaviors beyond frank drug abuse
• This presentation reports the results of a systematic review completed to evaluate the evidence for often recommended risk reduction strategies to prevent aberrant drug-related behaviors
• Aberrant drug-related behaviors include any behavior that suggest nonmedical use of a drug and/or addiction.

• Common opioid-related aberrant drug related behaviors include: altering the route of delivery, obtaining opioids from inappropriate sources, unsanctioned use, drug seeking behavior, patient statements and other behaviors.
Common Aberrant Behaviors

• Altering route of delivery
• Obtaining opioids from other sources
• Unsanctioned use
• Drug Seeking
• Patient Statements
• Other Behaviors
Altering Route of Delivery

- Crushing tablet to facilitate rapid release from tablet
- Extraction in fluid for injection
- Alteration of drug for intranasal use
Obtaining Opioids from Other Sources

- Diverted medications
- Doctor shopping
- Stealing from another patient’s prescription
- Borrowing drugs from another patient
- Obtaining from nonmedical sources (e.g. drug dealers)
Unsanctioned Use

- Taking more OR taking less than the prescribed does
- Unauthorized dose escalations
- Bingeing
- Removing all or part of a supervised dose from the dosing site
- Stockpiling
Drug Seeking

- Patient requests for higher doses
- Recurrent prescription losses
- Repeated requests for faxed prescriptions or urgent appointments
- Claims that “nothing else works”
- Requests for specific drugs or brands
- Prescription forgery
Patient Statements

• Acknowledgement of addiction
• Admission of mood-elevating opioid effects
• Acknowledgment of withdrawal symptoms
• Resistance to changing therapy despite evidence of physical or psychological problems
Other Behaviors

- Concurrent use of other legal and/or illicit drugs
- Selling or diversion
- Missed prescriber appointments
- Evidence of functional deterioration
Risk Reduction Strategies Evaluated

- Completion of a thorough patient assessment (history and physical)
- Assessment of the risk for substance abuse
- Use of controlled-substance agreements
- Selection of an appropriate and careful dose titration
- For most patients, observance of an opioid dose ceiling
Risk Reduction Strategies Evaluated
(continued)

- Use of formulations designed with impediments to tampering
- Compliance monitoring (e.g. pill counts and urine screens)
- Adherence to practice guidelines
- Compliance with regulatory and legal measures
Search Methods

• Pub Med was searched under 9 general headings on January 18, 2013 for English language clinical trials and practice guidelines published since 2008.
• Pain Society guidelines from the United States and Canada regarding opioid therapy for chronic noncancer pain
• Articles published over 5 years ago were also considered
Levels of Evidence

• Articles identified were graded on a scale adapted from the Oxford Centre for Evidence-Based Medicine Levels of Evidence:
  1. RCT with narrow CI/SR of RCTS: strong
  2. SR of cohort studies/Cohort Study/Low quality RCT: Moderate-strong
  3. SR of case control studies/Case control study: Weak to moderate
  4. Case series/Bench research/Expert opinion: Weak

CI: confidence interval; RCT: randomized controlled trial; SR: systematic review
Patient Assessment

- Medical history and examination to determine legitimate needs prior to treatment: LOE: 2
- Assessment of psychiatric comorbidity: LOE: 2
- Reassessment of analgesic needs and psychiatric comorbidities during treatment: LOE: 4
Patient Assessment - Comments

• Guidelines published in the US and Canada that recommend a thorough medical history and physical examination to establish the pain diagnosis, assess general medical condition and psychiatric status, and prior history of abuse are based on weak to moderate evidence that the strongest risk factors for current abuse are a history of abuse and psychiatric conditions.
• Level 2 evidence suggests that the majority of opioid abusers also have a history of abusing non-opioid substances including alcohol, nicotine and other legal and illegal drugs.

• Level 2 evidence suggests that it is important to identify psychiatric conditions known to be frequently comorbid with substance abuse such as depression, anxiety, bipolar disorder, and posttraumatic stress disorder.

• Several personality disorders (PD) have been associated with a risk of substance abuse including conduct disorder in adolescents, schizotypal PD, passive aggressive PD and borderline PD.

• Level 2 evidence suggests that a history of physical or sexual abuse is associated with an increased risk of substance abuse.

• Level 2 evidence suggests that contemplated or attempted suicide is also a risk factor for substance abuse.
Patient Reassessment During Treatment

• Although guidelines for safe, effective opioid use recommend that regular reassessments be conducted to identify behavioral or physical changes that may result from therapy, this recommendation is supported by weak evidence.

• Level 4 evidence suggests that abuse risk changes over time but the value of reassessment for preventing aberrant drug-related behaviors has not been demonstrated.
Assessment of the Risk for Substance Abuse

• Assessment at initiation of opioid therapy: currently available screening tools for the assessment of pretreatment opioid abuse risk include: the Current Opioid Misuse Measure (COMM), Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain – Revised (SOAPP-R) and the Prescription Drug Use Questionnaire

• Only weak evidence supports the utility of these instruments as stated in US and Canadian guidelines!
Assessment of the Risk for Substance Abuse - Comments

• Level 2 evidence suggests that risk factors included in the tools vary between population in ways that the screening tools do not pick up (older patients)

• Level 4 evidence suggests that additional risk factors such as legal problems, a history of victimization, mental and physical health status that are not identified in standard screeners
Use of Controlled-Substance Agreements

• US guidelines DO NOT recommend a controlled-substance agreement BUT Level 4 evidence (expert opinion) is cited suggesting that it may help to clarify the treatment plan with the patient, patient’s family, and others involved that patient’s care.

• Canadian guidelines DO recommend a controlled-substance agreement citing weak evidence.

• Level 2 evidence from a survey of 84 physician/patient pairs finds that controlled-substance agreements are likely to be used if the patient is considered at high risk for substance abuse.

• 40% of patients whose physicians reported that they had a controlled-substance agreement in place WERE UNAWARE OF this!
Use of Controlled-Substance Agreements - Comments

• The value of these agreements has not been established and may be limited by a lack of communication and consistency in their use.
Initial Opioid Selection and Dose Titration

First-line opioids:

• Canadian guidelines suggest that opioid therapy should start with a lower potency opioid (codeine/tramadol) based upon Level 2-3 evidence suggesting that there is a lower likelihood of abuse compared to higher potency opioids

• US guidelines do not comment about this in any detail
High potency opioids:
• Level 1 evidence has been cited that oxycodone has more positive subjective effects compared with equianalgesic doses of morphine
• Level 2 evidence noted that oxycodone, hydromorphone and hydrocodone have similar abuse liability
• US guidelines suggest that there is insufficient evidence to support the use of long-acting formulations over short acting for chronic pain
• Canadian guidelines suggest the use of long-acting opioids for chronic pain citing level 4 evidence
Dose titration- Canadian guidelines recommend initial doses of 5-10mg of morphine four times daily with incremental doses of 5-10mg/week- the preferred dose will result in a ≥ 2-point reduction in pain intensity rating on a 0-10 scale and/or a similar improvement in function.

Level 4 evidence suggests that this method might prevent administration of unnecessarily high opioid doses.

Level 1 evidence in a cohort of veterans with chronic pain found NO difference in the occurrence of aberrant drug-related behaviors between patients held on a stable dose and those using a more liberal dose-escalation approach.
Opioid Dose Ceiling

- 2009 US and 2011 Canadian guidelines state that doses above a morphine-equivalent (MED) of 200mg/day are considered “high”
- American Society of Interventional Pain Physician Guidelines state a MED of greater than 90mg/day is “high”
- Consistent Level I evidence suggests that higher doses have been associated with an increased risk of overdose and mortality
- Level 2 evidence suggests that the imposition of the 120mg/day MED ceiling in Washington state was accompanied by a 50% reduction in opioid related mortality in that state
Formulations Designed with Impediments to Abuse

• Level 1 and Level 2 data support the value of reformulated oxycodone CR as being less attractive for abuse than the older formulations

• NAVIPPRO data suggests that oxycodone CR abuse declined by 30% during the 20 months after the introduction of the reformulated tablet (however also noted was increased abuse of oxymorphone ER and buprenorphine during the same time)

• Level 4 evidence has been presented regarding the value of the reformulated oxymorphone ER in deterring tampering

• Level I evidence has been presented demonstrating that the abuse liability of oxycodone IR with aversive ingredients is less than conventional oxycodone IR

NAVIPPRO: National Addictions Vigilance Interventions and Prevention Program
Compliance Monitoring

- Urine drug screening currently considered the most objective tool for monitoring and documenting treatment compliance BUT there is only level 4 evidence to support this.
- Additional compliance monitoring tools include pill and patch counts, pharmacy and caregiver feedback, prescription drug monitoring programs (state specific) and regular physician-patient interactions.
- US guidelines published in 2009 reported that there is no reliable evidence to support the efficacy of any of these approaches for detecting, preventing or modifying aberrant opioid-related behaviors.
- ASIPP guidelines however state that the evidence is good!
- Level I evidence suggests that combining urine screening with pill counts, treatment agreements and patient education reduced substance abuse by 50%.
Compliance Monitoring (continued)

• Level 2 evidence suggests that urine screening can aid in distinguishing between overuse and underuse in many patients prescribed opioids for chronic pain

• Level 2 evidence suggests that a survey suggests the majority of physicians have a poor understanding of how to interpret urine drug screening results
Compliance with Pain Management Guidelines

Does compliance with clinical guidelines mitigate risk of opioid abuse?

• Level 3 evidence suggests that many clinicians do not routinely perform appropriate compliance monitoring

• A level 1 study suggests that many clinicians may lack adequate understanding of how to interpret compliance monitoring results
Compliance with Pain Management Guidelines (continued)

• Guideline recommendations on responding to aberrant drug-related behaviors

• Guidelines (US and Canadian) cite weak- moderate evidence to recommend that patients with suspected opioid misuse should be administered opioids in a structured trial including no short-acting or parenteral opioids, more frequent than usual monitoring and dispensing- and that patients who fail a structured opioid trial, tamper with their medications, are addicted to other substances and/or acquire opioids from illegal sources may require referral to a specialty pain clinic or for formal addiction counseling.

• Level 2 evidence suggests that a structure opioid trial may resolve aberrant drug-related behavior
Legal and Regulatory Measures

- Level 4 evidence has been cited by a FDA advisory committee suggesting that FDA mandated REMS programs for extended release and long-acting opioids are not likely to have a major impact on abuse rates for a variety of reasons including:
  1) It is not a mandatory program
  2) Medication guides are already available
  3) Abuse is not likely to be reduced through this approach by those who obtain their opioids from a friend, relative or other source

- Level 4 evidence from physician surveys suggest that such REMS education while perhaps helping to reduce abuse, will place additional demands on a physician’s time. Additional level 4 evidence suggests that if made mandatory, many physicians would discontinue prescribing such opioids.

- As already stated, level 2 evidence shows that the dose ceiling imposed in the state of Washington has resulted in a 50% reduction in opioid –related mortality (1/3 reduction in opioid prescriptions)
Conclusions

- There is a great need given the growth of prescription opioid use and abuse to prevent, detect and manage aberrant drug-related behaviors.
- The quality of evidence used to support published guidelines is generally weak to moderate for single tools used to accomplish the above.
- Given that the evidence the use of a combination of available approaches may be helpful, it is essential that clinicians prescribing opioids use all available tools in hope that their combination will prevent as much opioid abuse as possible.
- As regulators, legislators and others consider potentially austere measures to limit opioid drug abuse by severely limiting opioid prescribing, we need to be careful that such measures do not compromise effective pain management and increase suffering for those patients with chronic pain who truly need and safely benefit from opioid therapy.
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