Emerging Clinical Challenges in Prescribing Buprenorphine

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Overview

- Prescribing of buprenorphine to treat opioid dependence is increasing
  - Patients are benefiting from office-based treatment
  - Buprenorphine is well-accepted by patients and effective for treatment of opioid addiction
- As more buprenorphine is prescribed reports of diversion are increasing
  - Press coverage that focuses on the negative aspects resulting in negative public perception
  - Potential for more restrictive regulation

Current Status

- 13,315 waivered physicians
- Up to 190,000 patients with opioid dependence have been prescribed buprenorphine
- Thousands have received effective treatment of their opioid dependence
- Access to treatment has been substantially increased
- Greatest use in Northeast (Vermont, Maine, Massachusetts, Rhode Island)
- Increasing numbers of physicians using Suboxone for treatment of pain (estimated at 5% currently)
  - No statistics on how many pain patients also have opioid addiction (but we can reasonably assume that a large amount of diverted analgesics (oxycodone, hydrocodone and methadone) are coming from such patients); these patients represent a diversion risk as well and may be more difficult to track

Recent Press Coverage

“…in the company study published October, its consultants found that half of the doctors they surveyed were aware of an illegal trade in buprenorphine and that their numbers have been climbing. The study concluded that: "It was the patients in treatment for opioid abuse - no doubt selling or trading their own supply of buprenorphine - who were seen as major contributors to the street supply."
Baltimore Sun Jan 17, 2008

“Baltimore's health commissioner told officials that addicts using the drug on the street mostly say they do so to avoid withdrawal, not to get high. "That is not the type of diversion that is a public health crisis,“… "It doesn't mean I support it."
Baltimore Sun Jan 25, 2008

A major source of illegal Suboxone, according to 17 percent of doctors surveyed, was "lax or inappropriate" prescribing of the drug by their peers. More than half the doctors questioned in New England, where Suboxone is most widely available as an addiction treatment, said they believed it was just as easy to buy illegally as methadone and other widely abused narcotics. Drug abusers who were interviewed generally agreed.

• Interviews with drug treatment clients in Lynn, Mass., suggested that growing numbers of drug abusers might be turning to Suboxone to get high. In past reports, company officials have said 90 percent of people abusing Suboxone buy it on the street to ward off symptoms of narcotics withdrawal. But a third of the drug abusers questioned in Massachusetts said they used the drug to get high.

In Vermont, a researcher reported that 14 percent of prescription opioid abusers reported that buprenorphine was their "primary opioid of abuse." Baltimore Sun 2/3/08

Art Bessette and his wife are still grieving the loss of his 30-year-old son, Chad, who died after mixing alcohol, buprenorphine and the muscle relaxer cyclobenzaprine at a bachelor party last year. The Bessettes live in Burlington, Vt. (Sun photo by Doug Kapustin / October 12, 2007)

Vice squad Lt. Timothy O'Connor examines tablets of Suboxone taken from the streets of Worcester, Mass. (Sun photo by Doug Kapustin)

Emerging Issues*

- By 2007, 45% of physicians report knowing of diverted BUP
- 11% know of doctor shopping
- 34% think it's easier to get BUP than methadone on the street
- 33% think it's easier to get BUP than Oxycontin on the street
- Most physicians think diversion is related to self medication of withdrawal (41% v. 7% to 'get high')
- Physicians ideas about diverted BUP
  - Addicted patients: 46%
  - Pain patients: 12%
  - Inappropriate prescribing: 17%
  - Theft: 5%

  - Surveillance Report, CRS Associates 12/07

Emerging Issues*

- ED visits related to BUP 2003 (1) v 2007 (Q1-3) 368 (compared to nearly 6000 for methadone and 9,000 for oxycodone)
- Toxic exposures to BUP: higher in children (2%) than for methadone, oxycodone or heroin (0.5%)
- 27% of toxic BUP exposures reported by Poison Control Centers occurred in children under 6 yrs
  - (methadone: 7%, oxycodone: 8%)
- 6 deaths 2006-7

Emerging Issues

- Political fallout
  - Calls for hearings by various senators: Kerry, Sanders (has now asked for hearings after learning that SAMHSA knew of problems in Vermont since 2005, but only released report in Jan. 2008)
  - FDA “will evaluate and determine what, if any, regulatory action is warranted” C. Kelly, FDA

Areas that may need modification: Treatment Dose

- Limited evidence for the 32 mg sublingual dose
  - 1 clinical trial comparing LAAM 75-115 mg, 16-32 mg BUP,60-100 mg methadone or 20 mg methadone (Johnson et al. 2000)
  - PI recommends 12-16 mg/d based on clinical trials data
  - Little experience with 32 mg dose in clinical trials; qod dosing studies
    - Clinical Pharmacology studies:
    - PK 8 mg solution v 16 mg tablet (chronic dosing showed relative bioavailability of the tablet to be .71 of solution (Compton et al. 2006)
    - Harris et al 2004 report lack of dose proportionality for single doses of solution (4, 8, 16, 32 mg) and tablet (4/1, 8/2, 16/4 mg) and no differences in between dose strengths for most subjective and physiological effects
    - Single dose PK 4/1, 8/2, 16/4, 24/3 mg Suboxone showed respiratory rate, pupil diameter, subjective effects did not increase with increasing doses (Ciraulo et al 2006)
    - Blockade efficacy of bup/nx increases with increasing dose, but 32/8 provides only partial blockade following agonist administration (Strain et al. 2002)

Areas that may need modification: Physician Training

- Little training in medical school or residency in addiction medicine
- Is 8 hours of training enough?
  - Current trainings need to be updated to include more recent studies and diversion information
  - Additional courses for those with less experience in addiction
  - Regular web-based conferences for those who take on-line or CDROM courses
  - Mentors/practicum
  - Firmer guidelines needed:
    - **Dosing**
    - **Office visits**
    - **Urine drug screening**
    - **Adjunctive treatments**
    - **Inclusion of pill counts (+ UDS doesn't mean diversion isn't occurring)**

Areas that may need modification: Allied Provider Training

- Non-physicians receive little training in treatment of SUDs
- No requirement for allied providers that may be involved in practices offering buprenorphine treatment to receive any training—even though they may be the principal provider seen at a visit
- ATTCs have a 6 hour training—not easy to find online; use is unclear

Research

- Studies to look at treatment outcomes by dose
- Neuroimaging: extent of BUP binding of opioid receptors by dose
- Studies of sublingual BUP for chronic pain to establish practice guidelines
- Better understanding of drug interactions
  - Should alcohol be a contraindication?
  - What about benzodiazepines?
  - Psychotropics (e.g.: sedating antidepressants)
  - Muscle relaxants
- Ongoing determination of sources of diverted drug

Federal Agencies

- Need to be perceived as keeping public informed about health/safety issues
- Need to inform physicians/allied providers about problems with office-based treatment as they become known
- Encourage/assist with establishment of prescription monitoring systems
- Dissemination/education

REFERENCES

Chiang, C.N., Hawks, R.L., 2003. Pharmacokinetics of the combination tablet of buprenorphine and naloxone. Drug Alcohol Depend 70, S39-S47.

Ciraulo, D.A., Hitzemann, R.J., Somoza, E., Knapp, C.M., Rotrosen, J., Sarid-Segal, O., Ciraulo, A.M., Greenblatt, D.J., Chiang, C.N., 2006. Pharmacokinetics and pharmacodynamics of multiple sublingual buprenorphine tablets in dose-escalation trials. J Clin Pharmacol 46, 179-192. .

Compton, P., Ling, W., Chiang, N., Moody, D.E., Huber, A., Charuvastra, C., 2007. Pharmacokinetics of buprenorphine: a comparison of sublingual tablet versus liquid after chronic dosing. J Addict Med 1, 88-95.

Compton, P., Ling, W., Moody, D., Chiang, N., 2006. Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. Drug Alcohol Depend 82, 25-31.

Greenwald, M.K., Schuh, K.J., Hopper, J.A., Schuster, C.R., Johanson, C.E., 2002. Effects of buprenorphine sublingual tablet maintenance on opioid drug-seeking behavior by humans. Psychopharmacol 160, 344-352.
Harris, D.S., Mendelson, J.E., Lin, E.T., Upton, R.A., Jones, R.T., 2004. Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with nalaxone: lack of dose proportionality. Clin Pharmacokinet 43, 329-340.
Hopper, J.A., Wu, J., Martus, W., Pierre, J.D., 2005. A randomized trial of one-day vs. three-day buprenorphine inpatient detoxification protocols for heroin dependence. J Opioid Manag 1, 31-35.
Jagsch, R., Gombas, W., Schindler, S.D., Eder, H., Moody, D.E., Fischer, G., 2005. Opioid plasma concentrations in methadone- and buprenorphine-maintained patients. Addiction Biology 10, 365-371.
Johnson, R.E., Chutuape, M.A., Strain, E.C., Walsh, S.L., Stitzer, M.L., Bigelow, G.E., 2000. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med 343, 1290-1297.
.

McAleer, S.D., Mills, R.J., Polack, T., Hussain, T., Rolan, P.E., Gibbs, A.D., Mullins, G.P., Hussein, Z., 2003. Pharmacokinetics of high-dose buprenorphine following single administration of sublingual tablet formulations in opioid naïve healthy male volunteers under a naltrexone block. Drug Alcohol Depend 72, 75-83.
Nath, R.P., Upton, R.A., Everhart, E.T., Cheung, P., Shwonek, P., Jones, R.T., Mendelson, J.E., 1999. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. J Clin Pharmacol 39, 619-623.
Petry, N.M., Bickel, W.K., Badger, G.J., 2000. A comparison of four buprenorphine dosing regimens using open-dosing procedures: is twice-weekly dosing possible? Addiction 95, 1069-1077.
Schuster, CR: National findings, buprenorphine surveillance report. CRS Associates, 1210/07.
Strain, E.C., Walsh, S.L., Bigelow, G.E., 2002. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. Psychopharmacol 159, 161-166.
Wilford B Maxwell JC, and JBS International and Gulf Coast ATTC: Diversion and abuse of buprenorphine: a brief assessment of emerging indicators. Report to CSAT, 11/30/06