BuTrans Patch
Buprenorphine Transdermal System (BTDS) for Weekly Application

Classification
(Semisynthetic, highly lipophilic opioid; derivative of morphine alkaloid thebaine; brain tissue levels far exceed serum levels)
- Individualization & reassessment.
- RxFiles Q&A Summary

Estimated Dose Equivalencies: BuTrans (BTDS) may be 25–110x more potent than oral morphine; individual variance: highly controversial!!!

Note however that opioid withdrawal may occur for patients taking long-term and/or higher doses of opioids after switching to buprenorphine!!

Cost / 4 weeks:
- 5mcg/hr: $60
- 10mcg/hr: $105
- 20mcg/hr: $185

Currently not covered by most drug plans!

- AEs:
  - Breakthrough pain may be managed by acetaminophen or NSAID +/- codeine or other breakthrough meds per
  - Adverse Events (AE):
    - Adverse Events:
      - Discontinuation / Withdrawal:
        - Consider tapering if higher doses to reduce withdrawal symptoms; withdrawal generally mild & resolves in <2 weeks
        - After removal of patch, levels should steadily decrease, & should not exceed 50% over ~12 hours (10-24 hrs); administering a subsequent opioid after patch removal should only be delayed until 24 hours after removal
        - Other:
          - Steady state levels in ~3 days. Heat sources (external): Will ↑ absorption & risks (e.g. heat pad, hot bath, sauna, sunbathing, fever, etc.)
          - Advantages: long-acting useful for chronic-stable type pain; once-weekly application & kappa antagonist effect may result in less dysphoria, psychological craving & dependence [However, data from Norway suggests addiction concerns]. May cause less withdrawal when stopped than other opioids; incidence of constipation may be lower.
          - Compared to the fentanyl patch: lower abuse potential, mild withdrawal symptoms, may initiate in opioid naïve.
          - Disadvantages: long & delayed action means it is not suitable for acute or fluctuating pain; adverse effects may be sustained for >24 hours after removal of patch. [If one holds that it is a partial mu agonist, this would limit the opioid effect resulting in both a ceiling dose & potential withdrawal in patients dependent on other long-term opioids.]. Studies are short term (e.g. ≤12 weeks; most ≤4 weeks); results modest & benefits ± harms (NNT = 7-8 & NNH for ↑AE = 6-9).
          - CEDAC (Sept-2011 CDR Update): recommends against listing for coverage; high cost but no more effective than PO opioids

Therapy Use/Place in Strengths
- Persistent pain of moderate intensity in adults (≥40kg) requiring continuous opioid analgesia for an extended period of time (not suitable for unstable or widely fluctuating pain). Higher patch strengths e.g. TRANSDERMAL 35-70mcg/day (available in Europe for pain). ^
- Can be used in opioid naïve patients (alternate to codeine, tramadol) and patients previously only on prn opioids

Contraindications
- Hypersensitivity, GI (ileus, surgical abdomen), mild/intermittent/acute pain, acute asthma/obstructive airway/respiratory depression, acute alcoholism/dependence, opioid dependence/acute opioid withdrawal, convulsive disorders, MAOIs within 14 days, myasthenia gravis, hepatic insufficiency, pregnant/lactating: ≤40kg

Dose
- (Patch provides sustained levels & analgesia over 7 days.) (High affinity for mu receptor = blockade may last >7hrs. Effect not totally related to plasma levels.)
- Dosage: generally recommended after 7 days; and not more frequently than after 3 days.
- Maximum dose: 20mcg/hr. (Patch applied for 7 days.) Doses ≥40mcg may be associated with QT prolongation (but less than methadone).
- Breakthrough pain: may be managed by acetaminophen or NSAID +/- codeine or other breakthrough meds per
- Adjustments: Renal dysfx: NO dose adjustment required; (hepatic metabolism [acidification & biliary excretion]).
- Other:
  - Metabolism:
    - Buprenorphine is metabolized via CYP3A4 to nor buprenorphine (a metabolite).
  - Drug Interactions (DI): Metabolized via CYP3A4 to nor-buprenorphine (an active metabolite).
  - Metabolism:
    - Buprenorphine is metabolized via CYP3A4 to nor buprenorphine (an active metabolite).
  - Metabolism:
    - Buprenorphine is metabolized via CYP3A4 to nor buprenorphine (an active metabolite).
  - Metabolism:
    - Buprenorphine is metabolized via CYP3A4 to nor buprenorphine (an active metabolite).

Drug Interactions
- 3A4 inhibitors: ↑ dose related toxicity of buprenorphine e.g. amiodarone, itraconazole, clarithromycin, fluconazole, erythromycin, grapefruit juice, protease inhibitors ritonavir, nefazodone, etravirine, lamivudine, ditrazil

Adverse Events
- Common on initiation: nausea, diziness, somnolence, constipation, pruritus, dry mouth
- Most common in clinical trials: anorexia, site erythema/pruritus, rash (4%), insomnia, constipation, dizziness, dry mouth, headache, hyperhidrosis, nausea +/- vomiting, somnolence. [Potential QT prolongation with ≥240mcg/hr patch].
- Serious, but less common with careful dose titration: respiratory depression; however taking effect in respiratory depression, hypotension

Discontinuation / Withdrawal
- Consider tapering if higher doses to reduce withdrawal symptoms; withdrawal generally mild & resolves in <2 weeks
- After removal of patch, levels should steadily decrease, & should not exceed 50% over ~12 hours (10-24 hrs); administering a subsequent opioid after patch removal should only be delayed until 24 hours after removal
- Other:
  - Steady state levels in ~3 days. Heat sources (external): Will ↑ absorption & risks (e.g. heat pad, hot bath, sauna, sunbathing, fever, etc.)
  - Advantages: long-acting useful for chronic-stable type pain; once-weekly application & kappa antagonist effect may result in less dysphoria, psychological craving & dependence [However, data from Norway suggests addiction concerns]. May cause less withdrawal when stopped than other opioids; incidence of constipation may be lower.
  - Compared to the fentanyl patch: lower abuse potential, mild withdrawal symptoms, may initiate in opioid naïve.
  - Disadvantages: long & delayed action means it is not suitable for acute or fluctuating pain; adverse effects may be sustained for ≥24 hours after removal of patch. [If one holds that it is a partial mu agonist, this would limit the opioid effect resulting in both a ceiling dose & potential withdrawal in patients dependent on other long-term opioids.]. Studies are short term (e.g. ≤12 weeks; most ≤4 weeks); results modest & benefits ± harms (NNT = 7-8 & NNH for ↑AE = 6-9).
  - CEDAC (Sept-2011 CDR Update): recommends against listing for coverage; high cost but no more effective than PO opioids

Administration
- Apply to: non-irritated, dry, intact skin; upper arm, outer upper arm, upper back or side of chest (away from the umbilicus)
- Do not apply creams or ointments etc. to skin <6 hours prior to patch application as may affect adhesion.
- If site irritation, consider a corticosteroid spray (e.g. beclomethasone or fluticasone) to skin area prior to patch; (this lack of data & may affect absorption). [Alternatively, steroid cream post-patch or wet/dry heat pad may help adhesion].
- Rotate sites with each new patch; choose 4 or more sites and rotate; allow 3 weeks before reusing the same site
- Avoid exposure of patch to direct sunlight. Showering, swimming & bathing should not affect patch.

Strengths
- Patch (transdermal, 5mcg/hr 12.0gmbq/10), 10mcg/hr (0.24mg/day), 20mcg/hr (0.48mg/day); 15mcg/hr also now available

Use/Place in Therapy
- Opioid analgesic (mu agonist; kappa & delta antagonist). Narcotic and Controlled Drug (Canada).
- It is often considered a partial mu agonist; however some recent literature suggests full potent mu activity. Its action may more resemble a full mu agonist at lower doses, and partial mu agonist at higher doses. Controversial!
- (Note, a related product, SUBOXONE consists of [buprenorphine 2mg + naloxone 0.5mg] as a SL tablet used to treat opioid dependence. Bioavailability of buprenorphine-variable: Transdermal: 70%, SL: 30-70%: Suboxone usual dosage range is 4-24mg/day buprenorphine. The amount of opioid equivalency is uncertain; however, the 20mcg/hr patch is considered to be ≤50 MED. Only ~2% of the naloxone is absorbed; it will precipitate withdrawal if injected, in useful in OUD.
- Most are similar to other Adverse (AE)
- Metabolism:
  - Buprenorphine is metabolized via CYP3A4 to nor buprenorphine (an active metabolite).
  - Metabolism:
    - Buprenorphine is metabolized via CYP3A4 to nor buprenorphine (an active metabolite).
  - Metabolism:
    - Buprenorphine is metabolized via CYP3A4 to nor buprenorphine (an active metabolite).
### Table 1: Randomized controlled trials (RCT): buprenorphine transdermal system (BTDS) - BuTrans (7 day patch, chronic non-cancer pain)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Intervention</th>
<th>Results (primary: other)</th>
<th>Comments (general: industry-sponsored trials)</th>
</tr>
</thead>
</table>
| 1.11      | Low back pain, mod-sev (VAS ≥2/5) & not well controlled, (most had long hx) n=53 (26F; 25M); age ~54  | BTDS 5, 10, 20 mcg/hr or PI  + i i Acetaminophen 464 mg 4x pm  + DB, crossover  ↔ 7 wk  | • VAS: 37.6 +/- 20.7 vs 43.6 +/- 21.2  p=0.06  + of breakthrough pain: 1.8 vs 2.4/day  (NS)  | • Exclusions: multiple (e.g. if expected to exceed max bup dose) 79 patients enrolled; 53 patients evaluated per-protocol  
• most patients (59%) titrated to highest dose (litanies weekly) 82% of patients chose to continue for 6 month open label follow-up  |  |
| 1.12      | Low back pain, mod-sev, on prior opioid (78 randomized) PP. n=53 (20M; 39F); age ~51  | RRm 10, 20, 40 mcg/hr or PI  + i i Acetaminophen 464 mg 4x pm  + DB, crossover  ↔ 7 wk  | • Mean dose = 29.8 mcg/hr  + of PI  | BTDS had modest benefit vs PL considering prior opioid use  |  |
| 1.13      | Osteoarthritis (hip or knee); mod-sev; n=135  | BTDS Tramadol CR 150 - 400 mg/day  (acetaminophen pm 4x 2 wk)  + i i  | BS-11: no difference; -2.26 vs -2.09 (IT)  |  |
| 1.14      | Osteoarthritis (hip or knee); mod-sev; n=238 at run-in; 102 2% (analyzed)  & age ~64  | BTDS buprenorphine SR 0.2-4.0 mg q6h  + i i Acetaminophen 12 mg 1g pm  + DB, ↔ 4wks  | BS-11: scores considered equivalent (per protocol) for morning, midday & evening  |  |
| 1.15      | Osteoarthritis (hip or knee); n=315 at run-in;155% analyzed  & age ~60 (67%; 9)  | BTDS 10, 20 mcg/hr or PI  (no rescue medication allowed)  + i i  | 2.29% vs 3.4% (IT) satisfied  OR=1.66  |
| 1.16      | Osteoarthritis (hip or knee); n=588 at run-in; n=238 actually randomized  & age ~52 (76%); age ~67  | BTDS 10 mcg/hr or PI  vs placebo  (acetaminophen 12 mg 4x pm)  + DB, ↔ 16wks  | • patient satisfaction scale (0 – 4) at final visit  |  |
| 1.17      | Osteoarthritis (hip or knee); n=588 at run-in; n=53 (28%) severe pain  & age ~54  | BTDS 10, 20 mcg/hr or PI  (acetaminophen 12 mg 4x pm)  + DB, ↔ 16wks  | • patient satisfaction scale (0 – 4) at final visit  |  |
| 1.18      | Low back pain, mod-sev; n=119; age ~63  | BTDS 10, 20 mcg/hr or PI 6 mg  (acetaminophen)  vs placebo  + DB, ↔ 26wks  | • patient satisfaction scale (0 – 4) at final visit  |  |

### Select Studies with different dose (e.g. 35-70 mcg/hr) or dosage form (e.g. 3-day patch) than available in Canada; but of interest

| 1.25      | Chronic cancer pain  | BTDS 35 mcg/hr or PI  | pain  |  |
| 1.26      | Chronic cancer & non-cancer pain  | BTDS 35-70 mcg/hr or PI  | pain  |  |
| 1.27      | Chronic cancer & non-cancer pain  | BTDS 7.5-20 mcg/hr or PI  | pain  |  |
| 1.28      | Chronic cancer & non-cancer pain  | BTDS 10, 20 mcg/hr or PI  | pain  |  |

### Additional References & Links


### References

Prepared by Loren Regier, Sep 2010 (Update Dec 2011) for RxFiles Academic Detailing http://www.RxFiles.ca. Thanks to the many reviewers who provided input.

---

1. CPS 2010 Product Monograph - BuTrans
Comments (anecdotal) from clinicians on switching from other opioids to BuTrans

- Officially not recommended in Canada, but some experience has been positive
- Limited experience; if done, most success with tapering down the other opioids prior to switch to Butrans 5 or 10 and then titrated up as necessary. Direct opioid rotations mostly only for doses <40-60 mg/day of morphine.
- Encourage non-drug therapy complementary approaches in addition to drug therapy; essential for long term success of CNCP

- Relative potency for switching is not well established:
  - BuTrans 5 = .12 mg/day ≈ 10 mg/day morphine or 7.5 mg/day oxycodone
  - BuTrans 10 = .24 mg/day ≈ 20 mg/day morphine or 15 mg/day oxycodone
  - BuTrans 20 = .48 mg/day ≈ 40 mg/day morphine or 30 mg/day oxycodone

- Example- pt on 40 mg morphine (Meslon 20mg bid) with poor pain relief (VAS 8/10)
  - Option #1 (preferred?) Wean patient down to 20mg/day (10 mg am 15mg pm X 1-2 weeks the 15mg BID X 1-2 weeks the 10 mg am 15mg pm X 1-2 weeks then Sat am take last does of 10mg M-Eslon and apply BuTrans 10mg patch. Use MS-IR 5 mg bid prn for any withdrawal or severe pain
  - Option 2 = Patient on 20 mg M-Eslon bid; Sat am apply BuTrans 20 patch and take last dose of 20mg M-Eslon. Then use MS-IR 5-7.5 mg bid-tid severe pain or withdrawal.

[MS-IR = immediate release morphine sulphate]