Quintuple the daily maintenance dose of buprenorphine given every 5 days was associated with opioid withdrawal symptoms


**QUESTION:** In patients with opioid dependence, is quintuple the daily maintenance dose of buprenorphine (BUP) given every 5 days or triple doses every 3 days associated with more withdrawal symptoms than the daily maintenance dose?

**Design**

29 day randomised (unclear allocation concealment†), blinded (outcome assessors)*, crossover trial (study II).

**Setting**

Outpatient treatment clinic in USA.

**Patients**

17 patients (mean age: 35 y, 71% men) who were in good health and fulfilled DSM-III-R criteria for opioid dependence. Exclusion criteria were pregnancy, active psychosis, manic depressive illness, or serious medical illness (eg, liver or cardiovascular disease). 88% of patients completed the study.

**Intervention**

Patients received a maintenance dose of sublingual liquid BUP, 4 mg/70 kg daily (n=6) or 8 mg/70 kg daily (n=9), for 10 days. After the 10 days, patients received in a random order, each of the 3 dosing regimens: daily maintenance dose, triple every third day dosing, and quintuple every fifth day dosing. The daily dosing regimen was in effect for 5 days, and the other 2 regimens were in effect for 3 repetitions of each regimen.

**Main outcome measures**

Signs of opioid withdrawal (based on Addiction Research Center withdrawal scales), agonist activity assessed by observers, and computerised versions of the adjective rating scale (ARS) of withdrawal and drug symptoms, visual analogue scales (VAS), and the Addiction Research Center Inventory (ARCI) short form were completed by participants prior to receiving medication.

**Main results**

Withdrawal scores and VAS “sick” scores increased whereas VAS “drug” and VAS “high” scores decreased for both of the less frequent dosing regimens (table). In addition, in the every fifth day dosing regimen, scores of sedation and dysphoria were increased whereas scores of euphoria, stimulation and VAS “good” were reduced compared with the daily dosing regimen (table).

**Conclusion**

In patients with opioid dependence, quintuple the daily maintenance dose of buprenorphine given every 5 days was associated with more withdrawal symptoms and other negative effects than the daily maintenance dose.

*See glossary

**Observer and patient rated agonist and withdrawal effects for 3 buprenorphine dosing regimens in patients with opioid dependence†**

<table>
<thead>
<tr>
<th></th>
<th>Observer</th>
<th>Scale</th>
<th>Maximum</th>
<th>Daily maintenance</th>
<th>Triple, every third day</th>
<th>Quintuple, every fifth day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective withdrawal</td>
<td>Observer</td>
<td>9</td>
<td>0.25 (0.06)</td>
<td>0.37 (0.09)</td>
<td>0.70 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Subjective withdrawal</td>
<td>ARS</td>
<td>9</td>
<td>2.43 (0.45)</td>
<td>3.89† (0.71)</td>
<td>5.03 (0.68)</td>
<td></td>
</tr>
<tr>
<td>VAS high</td>
<td>VAS</td>
<td>100</td>
<td>8.39 (4.22)</td>
<td>2.60 (1.31)</td>
<td>2.09 (1.33)</td>
<td></td>
</tr>
<tr>
<td>VAS drug</td>
<td>VAS</td>
<td>100</td>
<td>10.55 (4.45)</td>
<td>4.00 (2.10)</td>
<td>2.51 (1.30)</td>
<td></td>
</tr>
<tr>
<td>VAS good</td>
<td>VAS</td>
<td>100</td>
<td>10.70 (4.15)</td>
<td>5.91 (3.66)</td>
<td>2.51 (1.36)</td>
<td></td>
</tr>
<tr>
<td>VAS sick</td>
<td>VAS</td>
<td>100</td>
<td>23.22 (4.93)</td>
<td>38.58 (7.94)</td>
<td>55.47 (6.77)</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>ARCI</td>
<td>15</td>
<td>6.01 (1.05)</td>
<td>7.61 (1.10)</td>
<td>9.56 (1.06)</td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>ARCI</td>
<td>13</td>
<td>5.87 (0.77)</td>
<td>7.08 (0.72)</td>
<td>8.31 (0.77)</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td>ARCI</td>
<td>14</td>
<td>3.70 (1.19)</td>
<td>2.89 (0.92)</td>
<td>1.61 (0.58)</td>
<td></td>
</tr>
<tr>
<td>Stimulation</td>
<td>ARCI</td>
<td>16</td>
<td>4.65 (0.77)</td>
<td>3.57 (0.74)</td>
<td>2.84 (0.69)</td>
<td></td>
</tr>
</tbody>
</table>

†Numbers are means (standard error). ARS—adjective rating scale; ARCI—Addiction Research Center Inventory short form; VAS—visual analogue scales. ‡Significantly different from daily maintenance dose (p<0.05).

**COMMENTARY**

This study by Petry et al provides information for clinicians regarding the maximal interdosing interval of BUP for the treatment of opioid addiction. The study showed the maximum interval to be < 5 days when 5 times the daily maintenance dose was given.

A number of factors will influence the degree to which less than daily dosing of BUP will be used in clinical practice. These include the patient’s response and acceptance, and the clinicians’ willingness and ability to prescribe take home medication doses (which in many cases could obviate the need for or advantages of less than daily dosing).

The greatest potential for less than daily dosing is likely to be for individuals for whom taking home dosing is not feasible. Patients who may be inclined to abuse or divert their prescribed medication may receive BUP on an every third day schedule (as in the present study), or twice weekly (as shown in previous studies by this research group).1 As noted by Petry et al, BUP and BUP/naloxone sublingual tablets have been developed, and are the BUP dosage forms that are (or will be, as more jurisdictions approve them)1 as noted by Petry et al, the use of the BUP/naloxone combination may itself decrease the abuse liability of BUP and therefore decrease the need for less than daily dosing.

Whether long term studies or clinical experience will confirm the utility of less than daily dosing has yet to be determined. This consideration will be particularly important in patient groups on higher daily BUP dosages (ie, > 8 mg/d of the sublingual solution or its equivalent), and in those who are not rewarded for remaining opioid abstinent (as they were in the present study).

Paul J Fudala, PhD

University of Pennsylvania/VA Medical Center

Philadelphia, Pennsylvania, USA


Quintuple the daily maintenance dose of buprenorphine given every 5 days was associated with opioid withdrawal symptoms

Evid Based Mental Health 2002 5: 21
doi: 10.1136/ebmh.5.1.21

Updated information and services can be found at:
http://ebmh.bmj.com/content/5/1/21

These include:

References
This article cites 3 articles, 0 of which you can access for free at:
http://ebmh.bmj.com/content/5/1/21#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Substance dependence (407)
Neurology (1070)
Substance withdrawal (18)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/