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 during 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.

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

<table>
<thead>
<tr>
<th>Outcomes at 29 days</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>Subjective withdrawal</td>
<td>Observer</td>
<td>ARS</td>
<td>9</td>
<td>0.25 (0.06)</td>
<td>0.37 (0.09)</td>
</tr>
<tr>
<td>VAS high</td>
<td>VAS</td>
<td>100</td>
<td>8.39 (4.22)</td>
<td>7.61 (4.00)</td>
<td>5.03 (0.68)</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>
</tr>
<tr>
<td>VAS good</td>
<td>VAS</td>
<td>100</td>
<td>10.70 (4.15)</td>
<td>9.51 (3.66)</td>
<td>2.51 (1.36)</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>
</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>
</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>
</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>
</tr>
<tr>
<td>Stimulation</td>
<td>ARCI</td>
<td>16</td>
<td>4.65 (0.77)</td>
<td>3.57 (0.74)</td>
<td>2.64 (0.69)</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 prescription medication may benefit from BUP on an every third day schedule (as in the present study), or twice weekly (as shown in previous studies by this research group). As noted by Petry et al, BUP and buprenorphine/naloxone sublingual tablets have been developed, and are the BUP dosage forms that are (or will be, as more jurisdictions approve them) used for the treatment of opioid addiction. A recent study reported that 3 times weekly dosing with BUP/naloxone sublingual tablets was associated with good patient acceptability, and provides encouragement that data obtained from studies evaluating less than daily dosing with the BUP sublingual solution will be clinically relevant. However, 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).

Source of funding: National Institutes of Health.

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

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