Opioid addiction: a paradigm shift in patient treatment, optimising outcomes

Friday 20th October 2017, 12:00–13:00
Auditorium, Bellevue Congress Centre
Faculty

**Professor Marc Auriacombe, MD**
Professor of Psychiatry and Addiction Medicine, Medical School of the University of Bordeaux, France and Adjunct Professor of Psychiatry at the University of Pennsylvania, Philadelphia, USA

**Professor Roberto Ciccocioppo, MD**
Professor of Pharmacology and Head of the International School of Advanced Study at the University of Camerino, Italy

**Dr Jan Melichar, MD**
Medical Director & Consultant Psychiatrist, Opioid Analgesia Dependency NHS Pilot, DHI, Bath and Consultant Psychopharmacologist, Glen Hospital, Bristol
Housekeeping

• Please turn mobile phones to silent
• Please remember to complete your evaluation forms to help us improve future educational meetings
• Discussions and questions are encouraged in the panel discussion at the end of the symposium
# Programme

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00</td>
<td>Chair’s introduction</td>
<td>Prof. Marc Auriacombe, France</td>
</tr>
<tr>
<td>12:05</td>
<td>Craving and its correlation with successful treatment outcomes</td>
<td>Prof. Marc Auriacombe, France</td>
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<tr>
<td>12:20</td>
<td>Buprenorphine pharmacology: the basics revisited</td>
<td>Prof. Roberto Ciccocioppo, Italy</td>
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<tr>
<td>12:35</td>
<td>Improving quality of life through personalised care</td>
<td>Dr Jan Melichar, UK</td>
</tr>
<tr>
<td>12:50</td>
<td>Interactive discussion</td>
<td>All</td>
</tr>
<tr>
<td>13:00</td>
<td>Meeting close</td>
<td></td>
</tr>
</tbody>
</table>
How to vote

• When a question appears on the screen, it will have numbered options
• Simply select your option and press the corresponding button
• If you wish to change your vote simply press your new selection
• Your last button pressed is the vote cast
Practice voting question

How many towns around the world is Biarritz twinned with?
A. 1
B. 3
C. 6
D. 8
Craving and its correlation with successful treatment outcomes

Professor Marc Auriacombe
Professor of Psychiatry and Addiction Medicine
University of Bordeaux, France
Disclosures

- D-A Pharma
- Lundbeck
- Indivior
- Gilead
- Bouchara
What is addiction? (or use disorder)

It’s not just using, even a lot

Opioid use disorder is a chronic medical condition affecting an estimated 1.3 million people across Europe

What is addiction?
Individual diagnostic criteria

- **ICD10 Dependence Syndrome**
  - At least 3 of the following within a year
  - a) Compulsion to use
  - b) Use is difficult to control
  - c) Withdrawal syndrome
  - d) Tolerance
  - e) Persistent use despite negative consequences
  - f) Reduced time for gratifying activities not related to drug use and increased time in drug-use-related activities

- **DSM 5 Use Disorder**
  - At least 2 of the following within a year
  1) Using more/longer than intended
  2) Persistent desire/unsuccessful efforts to cut down
  3) Time spent in substance activities
  4) Craving
  5) Failure to fulfill obligations
  6) Neglect of important activities
  7) Social/interpersonal substance-related problems
  8) Hazardous use
  9) Psychological/Physical use-related problems
  10) Tolerance
  11) Withdrawal

Define addiction and its consequences, and distinguish it from use.

A core … and a constellation

**Causes**
- Pre-existing factors
- Risk factors

**Loss of control**
- Relapse
- Craving

**Consequences**
- Use to excess
- Intoxication
- Withdrawal
- Toxicology
- Impairment

Is craving a consequence or a cause to use?
Voting question

Do you routinely measure craving in your daily clinical practice?

1. Yes
2. No
Craving predicts relapse

Over a period of months

3 months

Over a period of hours

3 hours

The craving-use relationship is dose-response

Let’s make it simple ...
Addiction: a disease (disorder) …

An objective sign: Relapse

A predictor symptom: Craving

Is craving just an intense desire or urge?

Oh, by the way, what’s the English for craving?

Unwanted craving
and it’s simple to measure

ÉVALUATION DU CRAVING

Défini comme une envie irrépressible de consommer et/ou comme la survenue de pensées obsédantes centrées sur l’objet d’addiction.

<table>
<thead>
<tr>
<th>Objets d’addiction</th>
<th>Fréquence</th>
<th>Intensité moyenne</th>
<th>Intensité maximale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nombre de jours sur 30 derniers jours</td>
<td>(avec l’échelle) sur 30 derniers jours</td>
<td>(avec l’échelle) sur 30 derniers jours</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>..../30</td>
<td>..../10</td>
</tr>
<tr>
<td>....................</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What should we do?

WHO International guidelines recommend that:

*Treatment of opioid use disorder should include pharmacological and psychosocial interventions*

Treatment is aimed at:

- Reducing or ceasing opioid use
- Preventing future harm associated with opioid use
- Improving quality of life and well-being for people with opioid use disorder

How can we best achieve those aims?
Clarified goals for medications

- **Primary goal**
  - Avoid relapse
  - Manage and reduce craving

- **Secondary goal**
  - Minimise opiate withdrawal symptoms

Treatment targets

Causes

Pre-existing factors
Risk factors

Loss of control
Relapse
Craving

Consequences
Use to excess
Intoxication
Withdrawal
Toxicology
Impairment

Methadone and buprenorphine
Psychotropic medications
A little medication and lots of psychotherapy

Auriacombe M et al. The Routledge Handbook of Philosophy and Science of Addiction 2017 (in press);
Medication efficacy on drug use reduction/abstinence is mediated by craving reduction in a dose-dependent relationship.

To conclude … and go on

- Clarify treatment targets
  - Confirm addiction
  - Clarify comorbidities: psychiatric and medical

- Control treatment success by optimal medication management and counseling
  - Appropriate counseling for craving monitoring
  - Appropriate dosing to manage craving

- … and most importantly
  - Share information with patients
Thank you

marc.auriacombe@u-bordeaux.fr

Université de Bordeaux

www.sanpsy.univ-bordeauxsegalen.fr
Buprenorphine pharmacology: the basics revisited

Professor Roberto Ciccocioppo
School of Pharmacy
University of Camerino, Italy
Disclosures

• Professor Ciccocioppo is the inventor of a number of patent applications, which have been assigned to Omeros, relating to the therapeutic use of PPARg agonists in addiction. He is entitled to receive royalties from Omeros under such licensing arrangement.

• Previous and current consultancy activities for Omeros Corporation, Takeda, Mitsubishi Tanabe, FB-Health, Cerevance
Objectives

1. Overview of current pharmacological treatments in opioid dependence
2. The pharmacodynamic effects of opioid receptor occupancy
3. Linking buprenorphine pharmacology to clinical outcomes
Objective

1. Overview of current pharmacological treatments in opioid dependence
### Approved treatments in opioid addiction

<table>
<thead>
<tr>
<th>TYPE OF TREATMENT</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
</table>
| Maintenance treatment (methadone, buprenorphine, SROM)| Strong evidence of capacity to:  
  ✓ Reduce opioid use  
  ✓ Decrease mortality  
  ✓ Improve quality of life  
  Capacity to retain patients in Rx | Expense to patient (daily travel dispensing fees)  
  Side effects, stigma  
  Prolonged withdrawal on cessation |
| Detoxification                                         | Short-term commitment  
  Attractive to consumer  
  Low threshold easy access  
  Entry point to treatment | Poor long-term outcomes if stand-alone treatment  
  Increased overdose risk following withdrawal  
  Can lead to destabilisation of other health conditions |
| Antagonist treatment (naltrexone, naloxone)            | Effective in decreasing opioid use in highly motivated well-supported people  
  Opioid-free medication | Poor retention for most people  
  Limited acceptance  
  Complicates pain management  
  Cost to patient  
  Requires detoxification prior to initiating naltrexone  
  Increased risk of overdose |

SROM, slow-release oral morphine  
## Opioids: Pharmacokinetic aspects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing route</th>
<th>Pharmacokinetic aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Oral (including slow release form), IV, IM, intrathecal</td>
<td>t_{1/2} = 3–4 hr; converted to active metabolite (morphine-6-glucuronide)</td>
</tr>
<tr>
<td>Heroin</td>
<td>IV, IM, smoked, oral chasing</td>
<td>t_{1/2} = &lt;1 hr; partly metabolised</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral, IV, IM</td>
<td>t_{1/2} = &gt;24 hr; not active metabolite</td>
</tr>
<tr>
<td>Pethidine</td>
<td>Oral, IM</td>
<td>t_{1/2} = 2–4 hr; active metabolite (norpethidine)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Sublingual, intrathecal, SC, IV, IM</td>
<td>t_{1/2} = 40 hr</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>IV, epidural, transdermal</td>
<td>t_{1/2} = 1–2 hr</td>
</tr>
<tr>
<td>Codeine</td>
<td>Oral</td>
<td>Acts as pro-drug; metabolised to morphine and other active opioids</td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous; t_{1/2}: the period of time required for the concentration or amount of drug in the body to be reduced by one-half.
Buprenorphine pharmacodynamics

Dose-response curves for three opioid painkillers

<table>
<thead>
<tr>
<th>Opioid receptor</th>
<th>Ki (nM)</th>
<th>Agonist/antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>1.5</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>δ</td>
<td>6.1</td>
<td>Antagonist</td>
</tr>
<tr>
<td>K</td>
<td>2.5</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Nociceptin or ORL1</td>
<td>77.4</td>
<td>Agonist</td>
</tr>
</tbody>
</table>

Receptor activation:
- Full agonist, partial agonist, antagonist

Euphoria and tolerance development is a function of ON-OFF effect and full agonist properties.
Question
Compared to full μ opioid receptor agonists, buprenorphine shows:

1. Less respiratory depression but similar reinforcing effects
2. Less respiratory depression and lower reinforcing effects
3. Similar respiratory depression and similar reinforcing effects
4. Higher respiratory depression and higher reinforcing effects
Objective

2 The pharmacodynamic effects of opioid receptor occupancy
Buprenorphine binds to NOP receptors

Buprenorphine is a semisynthetic opioid agent derived from thebaine\(^1\)

NOP plays a role in the regulation of reward and motivation pathways related to substance abuse\(^2\)

cAMP, cyclic adenosine monophosphate; NOP, nociceptin receptor; ORL1, opioid receptor-like 1
Buprenorphine occupation of μ-opioid receptors increases dose-dependently

- High-dose (>16 mg) buprenorphine maintenance produces near-maximal receptor occupation
- Higher receptor occupancy suppresses the effect of on-top hydromorphone use ("opioid blockade")

Buprenorphine 32 mg may not be licensed in all countries. Please prescribe in accordance with local policies. MRI, magnetic resonance imaging.

μ-opioid receptor occupancy decreases over the 76 hours after buprenorphine 16 mg dosing

Mean whole-brain μ-opioid receptor availability after buprenorphine*

- 82%
- 67%
- 54%
- 30%

*Relative to heroin-dependent volunteers maintained on placebo; Buprenorphine/naloxone is licensed for doses of up to 24 mg. Buprenorphine is licensed for doses of up to 32 mg. MRI, magnetic resonance imaging. Greenwald M et al. Biol Psychol 2007;61:101–10.
Withdrawal symptoms occur at <40–50% receptor availability, corresponding to a buprenorphine plasma concentration of <1 ng/mL.

Plasma levels after buprenorphine 16 mg dosing correlate with μ-opioid receptor occupancy.

<table>
<thead>
<tr>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>24-h AUC (ng/mL*h)</th>
<th>78-h AUC (ng/mL*h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9 (0.4)</td>
<td>2.2 (0.3)</td>
<td>21.7 (82)</td>
<td>41.9 (3.9)</td>
<td>75.4 (10.0)</td>
</tr>
</tbody>
</table>

AUC, area under the curve; C<sub>max</sub>, maximum plasma concentration; t<sub>max</sub>, time to reach C<sub>max</sub>; t<sub>1/2</sub>, half life

Buprenorphine 16 mg: μ-opioid receptor occupancy over time

<table>
<thead>
<tr>
<th>Brain region</th>
<th>BUP Placebo</th>
<th>4 h (μmax/Ƙd)</th>
<th>28 h (μmax/Ƙd)</th>
<th>52 h (μmax/Ƙd)</th>
<th>76 h (μmax/Ƙd)</th>
<th>Time (F Test)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>0.69 (0.01)</td>
<td>0.21 (0.02)</td>
<td>0.37 (0.03)</td>
<td>0.47 (0.03)</td>
<td>0.57 (0.03)</td>
<td>48.50</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Subgenual anterior cingulate (BA25)</td>
<td>1.39 (0.04)</td>
<td>0.43 (0.06)</td>
<td>0.83 (0.07)</td>
<td>1.04 (0.10)</td>
<td>1.30 (0.10)</td>
<td>35.45</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>2.09 (0.12)</td>
<td>0.65 (0.07)</td>
<td>1.27 (0.10)</td>
<td>1.51 (0.10)</td>
<td>1.80 (0.07)</td>
<td>53.55</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Rostral anterior cingulate (BA 32)</td>
<td>1.56 (0.04)</td>
<td>0.41 (0.06)</td>
<td>0.85 (0.08)</td>
<td>1.06 (0.09)</td>
<td>1.33 (0.09)</td>
<td>44.01</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Prefrontal cortex (BA 10)</td>
<td>1.19 (0.03)</td>
<td>0.34 (0.05)</td>
<td>0.64 (0.06)</td>
<td>0.83 (0.06)</td>
<td>1.01 (0.06)</td>
<td>44.37</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>1.90 (0.15)</td>
<td>0.52 (0.06)</td>
<td>1.03 (0.09)</td>
<td>1.28 (0.11)</td>
<td>1.53 (0.10)</td>
<td>48.17</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1.57 (0.08)</td>
<td>0.42 (0.05)</td>
<td>0.87 (0.08)</td>
<td>1.03 (0.08)</td>
<td>1.24 (0.09)</td>
<td>48.24</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.84 (0.08)</td>
<td>0.56 (0.05)</td>
<td>0.99 (0.07)</td>
<td>1.20 (0.08)</td>
<td>1.41 (0.07)</td>
<td>43.13</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

- Receptor occupancy >80% prevents the significant euphoric effects and respiratory depression elicited by on-top oxycodone (24 mg) administration i.e. blockade effect
- Receptor occupancy <40–50% – withdrawal signs appear

Blockade of opioid reward and craving may require higher doses (≥16 mg) than those needed to suppress withdrawal

- Suppression of withdrawal appears to require ≤50% of μ-opioid receptor availability
- For most patients, this requires single daily buprenorphine doses of 4 mg
- Blockade of the reinforcing and subjective effects of typical doses of abused opioids require <20% μ-opioid receptor availability
- For most patients, this requires single daily buprenorphine doses of >16 mg

What % of receptor occupancy is generally needed to have an anti-craving effect?

1. >80%
2. 70–80%
3. 60–70%
4. 50–60%
5. 40–50%
Objective

3 Linking buprenorphine pharmacology to clinical outcomes
Buprenorphine treatment reduces on-top use

- Flexible dosing and buprenorphine doses ≤6 mg are less effective than methadone at retaining patients in treatment

*Flexible dosing and buprenorphine doses ≤6 mg are less effective than methadone at retaining patients in treatment.*

Strong evidence that high dose of buprenorphine is associated with better retention in treatment

- Meta-analyses of 21 RCTs conducted between 1960 and December 2010
- Treatment duration ranged from 3 to 48 weeks

![Bar Chart]

- Patients (%) retained in treatment
- Higher dose (≥16 mg, avg dose 21 mg) vs Lower dose (<16 mg, avg dose 7.4 mg)
- p<0.006 favouring higher dose

Predictors of IOU: retention in treatment (↓ IOU); IOU, illicit opioid use; RCT, randomised controlled trial
Conclusions

• The unique characteristics of buprenorphine, namely, partial agonist effect, long duration of action and high binding affinity, make it an attractive treatment in opioid addiction

• Minimum μ-opioid receptor occupancy by buprenorphine of >40–50% prevents withdrawal symptoms but higher occupancy, typically >80% "blocks" euphoric effects from on-top opioid use and reduces craving symptoms

• Buprenorphine dose-dependently increases opioid receptor occupancy
  • High doses (≥16 mg) produce near-maximal occupancy, thereby providing an optimal occupation of opioid receptors
Improving quality of life through personalised care

Dr Jan Melichar  MD FRCPsych
Medical Director, DHI, Bath; Consultant Psychopharmacologist,
Glen Hospital, Bristol; Consultant Psychiatrist, NHS Opioid Analgesia
Dependency Service, South Gloucestershire, UK
Disclosures

• Dr Melichar has received honoraria and travel expenses from Indivior for delivering this presentation

• Dr Melichar has also received funding from another pharmaceutical company, Britannia Pharmaceuticals, to speak at symposia and conferences
How is QoL defined?

- Defined in many ways, making measurement difficult.
- The common principle is that it is patient-centered and mostly subjective.

QoL, quality of life
Jan Melichar, personal experience
Patients with OUD have a reduced HRQoL

- OUD is a chronic disorder with multi-faceted and negative medical, psychological and social consequences affecting various HRQoL domains\(^1\)

- Studies of HRQoL in patients with OUD have consistently found worse scores for physical and mental domains compared with the general population\(^3\)

- Questionnaires such as SF-36 or QLQ or LQoLP are used for HRQoL assessment

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**Comparison of SF-36 mean (pre-treatment) baseline scores from heroin-dependent patients versus Australian population norms\(^2\)**

<table>
<thead>
<tr>
<th>SF-36 domain scale</th>
<th>Heroin-dependent patients (n=326)</th>
<th>General population (n=4138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>38,0*</td>
<td>76,9*</td>
</tr>
<tr>
<td>Role limits – physical</td>
<td>48,8*</td>
<td>86,5</td>
</tr>
<tr>
<td>Pain</td>
<td>51,2*</td>
<td>81,5</td>
</tr>
<tr>
<td>General health</td>
<td>65,6</td>
<td>76,3</td>
</tr>
<tr>
<td>Vitality</td>
<td>45,5*</td>
<td>86,1</td>
</tr>
<tr>
<td>Social functioning</td>
<td>40,2*</td>
<td>86,2</td>
</tr>
<tr>
<td>Role limits – emotional</td>
<td>49,4*</td>
<td>76,2</td>
</tr>
<tr>
<td>Mental health</td>
<td>53,0</td>
<td>49,6</td>
</tr>
<tr>
<td>PCS</td>
<td>44,8</td>
<td>*p&lt;0.001 versus general population</td>
</tr>
<tr>
<td>MCS</td>
<td>32,6</td>
<td>49,6</td>
</tr>
</tbody>
</table>

HRQoL, health-related quality of life; LQoLP, Lancashire Quality of Life Profile; OUD, opioid use disorder; MCS, mental component summary; PCS, physical component summary; QLQ, Quality of Life Questionnaire; SD, standard deviation; SF-36, short form 36

Why do people seek treatment for OUD?

• Data from EQUATOR analysis of 2,298 patients and 887 out-of-treatment opioid users from 10 European countries

• A key factor in the treatment of OUD is the ability and willingness of patients to enter and remain in treatment

EQUATOR, European Quality Audit of Opioid Treatment; OUD, opioid use disorder
Interactive question

Based on 2017 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) data, approximately what percentage of patients with OUD across Europe are currently in treatment?

A. 30%
B. 40%
C. 50%
D. 60%
What are the barriers to seeking treatment for OUD?

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Proportion of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would still like to use drugs sometimes</td>
<td>30,3</td>
</tr>
<tr>
<td>Concern that wouldn't be able to follow the rules</td>
<td>29,9</td>
</tr>
<tr>
<td>Concern that wouldn't be able to make it through therapy</td>
<td>29,3</td>
</tr>
<tr>
<td>Waiting list to get treatment in my area</td>
<td>25,6</td>
</tr>
<tr>
<td>Dislike what I hear about treatment programmes</td>
<td>17,8</td>
</tr>
<tr>
<td>Concerned that family/friends/employer will find out</td>
<td>13,3</td>
</tr>
<tr>
<td>Can't find access in my area</td>
<td>13,1</td>
</tr>
<tr>
<td>Cost</td>
<td>12,1</td>
</tr>
<tr>
<td>Had bad experience last time, so won't repeat</td>
<td>11,6</td>
</tr>
<tr>
<td>Don't want to stop/happy with lifestyle</td>
<td>10,6</td>
</tr>
<tr>
<td>Lack of information/don't know enough about treatments</td>
<td>9,0</td>
</tr>
<tr>
<td>Don't know whom to talk to in order to obtain place in programme</td>
<td>7,5</td>
</tr>
<tr>
<td>Don't know whom to talk to in order to obtain place in programme</td>
<td></td>
</tr>
</tbody>
</table>

*Patients were asked to tick all that applied

- Data from EQUATOR analysis of 2,298 patients and 887 out-of-treatment opioid users from 10 European countries

EQUATOR, European Quality Audit of Opioid Treatment; OUD, opioid use disorder
Role of OAT in improving patients’ HRQoL

- Reduction in drug use and withdrawal symptoms
- Increased access to psychosocial support
- Decreased drug-seeking behaviour
- Increased access to pharmacological treatment for comorbid conditions

OAT, opioid agonist therapy; HRQoL, health-related quality of life
Interactive question

In what proportion of your patients do you routinely try to ascertain quality of life indicators?

1. 20–40%
2. 40–60%
3. 60–80%
4. 80–100%
Impact of psychosocial interventions on QoL

• OATs are approved for use within a framework of medical, social and psychological support as part of comprehensive treatment programme

• Goal of psychosocial treatment is to help patients control cravings and remain abstinent, while also helping them cope with the emotional burden of OUD

• Systematic review of studies on the use of psychosocial interventions in conjunction with OAT

Methadone
• 14 studies provided support for the use of psychosocial interventions with methadone treatment
• 9 studies showed a significant effect on treatment attendance and drug use
• 7 studies showed a significant effect on psychosocial functioning

Buprenorphine
• Evidence to support the efficacy of psychosocial interventions with buprenorphine treatment was less robust
• 3 studies reviewed found a significant effect on treatment attendance and drug use
• 1 study found a significant effect on 12-step/self-help meeting attendance

OAT, opioid agonist therapy; OUD, opioid use disorder; QoL, quality of life
Improvement in QoL following long-term treatment with buprenorphine or methadone

- Cohort study of patients with OUD on buprenorphine (n=106) or methadone (n=107) followed from month 3 to month 12 of treatment

- At 3 months, the total QLQ score was significantly greater with buprenorphine vs methadone (299.62 vs 258.96, respectively; p=0.003)

- At 12 months, retention rates were comparable (78.3% vs 74.6% for buprenorphine and methadone, respectively)

- At 12 months, statistically significant improvements in reduction in opioid use, psychiatric status, and general QoL* were observed with both treatments

*Assessed using the CGI, GAF Scale, SCL-90 and QLQ

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Comparison of QoL scores from buprenorphine- or methadone-treated patients

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine group (n=83)</th>
<th>Methadone group (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean urinalysis</td>
<td></td>
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</tr>
<tr>
<td>for opioids</td>
<td>65.94</td>
<td>78.30 **</td>
</tr>
<tr>
<td></td>
<td>78.30 **</td>
<td>92.98 **</td>
</tr>
<tr>
<td>DSM-IV</td>
<td></td>
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</tr>
<tr>
<td>GAF index</td>
<td>68.73</td>
<td>76.88 **</td>
</tr>
<tr>
<td></td>
<td>64.90 **</td>
<td>71.52 **</td>
</tr>
<tr>
<td>CGI – global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>improvement</td>
<td>1.74 **</td>
<td>2.42 **</td>
</tr>
<tr>
<td>SCL-90 global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>score index</td>
<td>0.34</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>0.65</td>
<td>0.57 **</td>
</tr>
<tr>
<td></td>
<td>**p&lt;0.01 versus 3 months</td>
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</tr>
</tbody>
</table>

OUD, opioid use disorder; QLQ, Quality of Life Questionnaire; QoL, quality of life; SD, standard deviation; SF-36, short form 36
‘The ACMD wishes to state that service users should receive opioid substitution medication doses in line with UK clinical guidelines, and sub-optimal opioid prescribing is unlikely to help service users stop illicit heroin use and is associated with poorer outcomes’
Rapid induction with buprenorphine improves initial retention in treatment and optimal dosing reduces craving.

Retention at 4 weeks (%)

0 - 20
20 - 40
40 - 60
60 - 80
80 - 100

Time (in days) to reach at least 8 mg of buprenorphine

0 - 8

Kakko et al. 2003
Amadi et al. 2004
Petitjean et al. 2001
Fudala et al. 2003
Fischer et al. 1999
Pani et al. 2002
Ortner et al. 2004
Gerra et al. 2004
Krook et al. 2002

Speed of induction should be guided by the patient’s level of opioid withdrawal.

Optimal dosing of OAT prevents relapse

• Higher doses of buprenorphine or methadone are significantly more effective than low doses at reducing illicit heroin use\(^1\)

• Higher maintenance doses of buprenorphine lead to improved outcomes\(^2\)

Higher maintenance doses of buprenorphine are associated with higher retention and increased abstinence from illicit opioids\(^3\)

*Joint probability score: measure of the likelihood of patients remaining in treatment and being drug-free; OAT, opioid agonist therapy
Buprenorphine receptor occupancy – importance of 16 mg dose

Relative to placebo, buprenorphine 16 mg reduced µ-opioid receptor availability in the brain.

- Reduced withdrawal symptoms and cravings
- Clarity of thought & other HRQoL benefits

HRQoL, health-related quality of life.
Factors impacting on drug-related deaths: Medically-assisted treatment

- 122,885 patients treated with methadone over 1.3–13.9 years
- 15,831 people treated with buprenorphine over 1.1–4.5 years
- Retention in methadone and buprenorphine treatment was associated with substantial reductions in the risk for all-cause and overdose mortality

<table>
<thead>
<tr>
<th>Methadone</th>
<th>In treatment</th>
<th>Out of treatment</th>
<th>All-cause mortality rate/1000 person years (95% CI)</th>
<th>All-cause mortality rate/1000 person years (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Gearing et al. 1974</td>
<td>110/14,474</td>
<td>33/1170</td>
<td>7.6 (6.2 to 9.2)</td>
<td>28.2 (19.4 to 39.6)</td>
</tr>
<tr>
<td>Cushman 1977</td>
<td>25/1655</td>
<td>14/297</td>
<td>15.1 (9.8 to 22.3)</td>
<td>47.1 (25.8 to 79.1)</td>
</tr>
<tr>
<td>Grönbladh et al. 1990</td>
<td>16/1085</td>
<td>32/740</td>
<td>14.8 (8.4 to 23.9)</td>
<td>43.2 (29.6 to 61.0)</td>
</tr>
<tr>
<td>Caplehom et al. 1994</td>
<td>11/1975</td>
<td>36/2279</td>
<td>5.6 (2.8 to 10.0)</td>
<td>15.8 (11.1 to 21.9)</td>
</tr>
<tr>
<td>Fugelstad et al. 1995</td>
<td>8/242</td>
<td>5/45</td>
<td>33.1 (14.3 to 65.1)</td>
<td>111.1 (36.1 to 259.3)</td>
</tr>
<tr>
<td>Fugelstad et al. 1998</td>
<td>7/177</td>
<td>4/57</td>
<td>39.5 (15.9 to 81.4)</td>
<td>69.9 (19.1 to 179.0)</td>
</tr>
<tr>
<td>Scherbaum et al. 2002</td>
<td>18/1114</td>
<td>14/172</td>
<td>16.2 (9.6 to 25.5)</td>
<td>81.4 (44.5 to 136.6)</td>
</tr>
<tr>
<td>Fugelstad et al. 2007</td>
<td>77/3354</td>
<td>74/1311</td>
<td>23.0 (18.1 to 28.7)</td>
<td>56.5 (44.3 to 70.9)</td>
</tr>
<tr>
<td>Clausen et al. 2008</td>
<td>90/6450</td>
<td>46/1303</td>
<td>14.0 (11.2 to 17.1)</td>
<td>35.3 (25.9 to 47.1)</td>
</tr>
<tr>
<td>Dagenhardt et al. 2009</td>
<td>648/111,538</td>
<td>1510/105,735</td>
<td>5.8 (5.4 to 6.3)</td>
<td>14.3 (13.6 to 15.0)</td>
</tr>
<tr>
<td>Cornish et al. 2010</td>
<td>30/5129</td>
<td>71/4288</td>
<td>5.8 (4.0 to 8.3)</td>
<td>16.6 (12.9 to 20.9)</td>
</tr>
<tr>
<td>Peles et al. 2010</td>
<td>42/3985</td>
<td>52/727</td>
<td>10.5 (7.6 to 14.2)</td>
<td>71.5 (53.4 to 93.8)</td>
</tr>
<tr>
<td>Evans et al. 2015</td>
<td>163/25,277</td>
<td>848/48,122</td>
<td>6.4 (5.5 to 7.5)</td>
<td>17.6 (16.5 to 18.8)</td>
</tr>
<tr>
<td>Kimber et al. 2015</td>
<td>636/92,792</td>
<td>563/45,265</td>
<td>6.9 (6.4 to 7.5)</td>
<td>12.4 (11.4 to 13.5)</td>
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<td>Nosyk et al. 2015</td>
<td>89/3979</td>
<td>206/1582</td>
<td>22.4 (18.0 to 27.5)</td>
<td>130.2 (113.0 to 149.3)</td>
</tr>
<tr>
<td>Cousins et al. 2016</td>
<td>115/22,648</td>
<td>98/6247</td>
<td>5.1 (4.2 to 6.1)</td>
<td>15.7 (12.7 to 19.1)</td>
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Overall: 11.3 (8.4 to 15.2) 36.1 (24.5 to 53.3)

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<td>Cornish et al. 2010</td>
<td>7/740</td>
<td>10/751</td>
<td>9.5 (3.8 to 19.5)</td>
<td>13.3 (6.4 to 24.5)</td>
</tr>
<tr>
<td>Reece 2010</td>
<td>3/1119</td>
<td>40/6911</td>
<td>2.7 (0.6 to 7.8)</td>
<td>5.8 (4.1 to 7.9)</td>
</tr>
<tr>
<td>Kimber et al. 2015</td>
<td>87/21,936</td>
<td>314/31,239</td>
<td>4.00 (3.2 to 4.9)</td>
<td>10.1 (9.0 to 11.2)</td>
</tr>
</tbody>
</table>

Overall: 4.3 (2.1 to 8.9) 9.5 (3.9 to 23.4)

CI, confidence interval; OAT, opioid agonist therapy
Adapted from Sordo L et al. BMJ 2017;357:j1550.
Summary

• OAT plays a key role in improving HRQoL by reducing drug use, withdrawal symptoms and drug-seeking behaviours, and increasing access to psychosocial support and treatment for comorbid conditions

• Routine assessment of HRQoL can add an important dimension to overall evaluation of patients’ response to OAT

• A personalised approach to care is needed with the optimal treatment strategy taking into account the patient’s complete medical and psychiatric history
  • Optimised dosing with buprenorphine reduces withdrawal symptoms and cravings, can improve initial retention in treatment and prevent relapse....

.....leading to improved HRQoL

HRQoL, health-related quality of life; OAT, opioid agonist therapy; OUD, opioid use disorder
Voting question

Do you routinely measure craving in your daily clinical practice?
• Yes
• No
Interactive discussion
Please remember to complete your evaluation form