The VEdeTTE national Italian cohort study:
Evaluation of effectiveness of treatments for heroin addiction in retaining patients and reducing mortality

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www.studio-vedette.it    www.oed.piemonte.it
Piedmont Centre for Drug Addiction Epidemiology
Torino (Italy)
Italian cohort study involving:

- **11905** heroin addicts in
- **13** Regions
- **115** NHS treatment centres
Main aims of the study

• To estimate treatment retention at 18 months according to
  • individual characteristics
  • type of treatment
  • association of treatments

• To evaluate mortality rate in relation with treatments

Key issue !!!
Enrollment

In the study period, were enrolled:

• all incident subjects: subjects starting a treatment in the centre for the first time
• all re-entry subjects: subjects starting a new treatment in the centre, but who had been previously treated in that centre
• all prevalent subjects: subjects under treatment at the beginning of the study
Standardized instruments

- **Questionnaire**: administered at the enrolment, contained questions on socio-demographic characteristics, legal problems, drug addiction history and drug use, overdoses, risk behaviours, HIV, HBV, HCV and other medical conditions. A few information about socio-demographic characteristics and heroin use were collected for not enrolled patients as well.

- **Treatment Registration Form**: type of treatment, starting and ending dates, dose, frequency, agreed conclusion or not. Information on treatments were collected all along the study period.

- **Centre Information Form**: information on the characteristics of the centre and its personnel
Characteristics of the cohort

Type of patients

- Incident: 11.9%
- Re-entry: 19.0%
- Prevalent: 69.1%
Characteristics of the cohort

Education

- < 6 years: 17.1%
- 8 years: 65.9%
- > 12 years: 16.7%
Characteristics of the cohort

Housing

- Parents: 54.8%
- Partner/children: 26.9%
- Friends/alone: 10.4%
- No fixed abode: 1.6%
- Therapeutic com.: 5.8%
Characteristics of the cohort

Job

- Stable: 33.5
- Unstable: 25.8
- Student: 1.0
- Other: 3.3
- Unemployed: 35.1
Characteristics of the cohort

Legal problems and imprisonment

- **Incident**
  - Legal problems: ~25%
  - Imprisonment: ~10%

- **Re-entered**
  - Legal problems: ~35%
  - Imprisonment: ~20%

- **Prevalent**
  - Legal problems: ~30%
  - Imprisonment: ~15%
### Characteristics of the cohort

#### History of addiction

<table>
<thead>
<tr>
<th></th>
<th>Men (n=8953)</th>
<th>Women (n=1501)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at enrollment</strong></td>
<td>31.2 years</td>
<td>30.6 years</td>
</tr>
<tr>
<td><strong>Age at first heroin use</strong></td>
<td>19.6 years</td>
<td>19.7 years</td>
</tr>
<tr>
<td><strong>Age at first treatment</strong></td>
<td>24.8 years</td>
<td>24.0 years</td>
</tr>
<tr>
<td><strong>Latency</strong> (First use/first treatment)</td>
<td>5.3 years</td>
<td>4.4 years</td>
</tr>
<tr>
<td><strong>Age at first overdose</strong></td>
<td>24.3 years</td>
<td>23.2 years</td>
</tr>
</tbody>
</table>
Characteristics of the cohort

Sharing needles or other instruments
Characteristics of the cohort

Prevalence of HIV, HBV, HCV

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>

p < 0.001

p < 0.30

p < 0.001
Treatment synthesis

40286 episodes of treatment
33831 index treatment
15197 therapies

Key issue !!!

Episodes of treatment of patient '05201' observed during the period of the study

Re-classification of treatments

index treatments
synthetic patterns of therapy
Treatments were classified in three main therapies:

<table>
<thead>
<tr>
<th>Therapeutic community</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone maintenance</td>
<td>MM</td>
</tr>
<tr>
<td>Tapering methadone</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td></td>
</tr>
<tr>
<td>Other pharmacological</td>
<td></td>
</tr>
<tr>
<td>Psychotherapy</td>
<td></td>
</tr>
<tr>
<td>Counselling</td>
<td></td>
</tr>
<tr>
<td>Job advices</td>
<td></td>
</tr>
</tbody>
</table>

AO = abstinence oriented therapies
Retention in treatment is considered a proxy of treatment effectiveness:

- Heroin addiction is a chronic condition (Leshner 1997, McLellan 2002)
- and treatments should last at least 2 years (McLellan 2002)
New patients, re-entry and prevalent patients have a different probability of staying in treatment: to avoid this possible bias.
Inclusion of therapies

Only:

- the first therapy for new and re-entry patients
- and the second therapy for prevalent patients

were included in the analysis (N= 5,457).

And

- prevalent and re-entry patients were considered as one category and named “re-entry patients”

Survival analysis and Cox Proportional Hazard models were used to evaluate treatment retention.
5,457 patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>New patients</th>
<th></th>
<th>Re-entry</th>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Methadone maintenance</td>
<td>530</td>
<td>43.6</td>
<td>1826</td>
<td>43.1</td>
<td>2356</td>
<td>43.2</td>
</tr>
<tr>
<td>Therapeutic community</td>
<td>82</td>
<td>6.7</td>
<td>493</td>
<td>11.6</td>
<td>575</td>
<td>10.5</td>
</tr>
<tr>
<td>Abstinence oriented therapies</td>
<td>604</td>
<td>49.7</td>
<td>1922</td>
<td>45.3</td>
<td>2526</td>
<td>46.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1216</td>
<td>100</td>
<td>4241</td>
<td>100</td>
<td>5457</td>
<td>100</td>
</tr>
</tbody>
</table>

Overall, the likelihood of remaining in treatment was 0.5 at 179 days
Characteristics of therapies

- **Therapeutic community**
  - N=575
  - 13.2% interrupted
  - 39.0% interrupted but followed by another therapy

- **Methadone maintenance**
  - N=2,356
  - Median daily dose: 37 mg/die
  - 17.5% interrupted
  - 28.1% interrupted but followed by another therapy

- **Abstinence oriented therapies**
  - N=2,526
  - 30.2% interrupted
  - 36.1% interrupted but followed by another therapy
New patients (n=1,216), $p<0.086$
KM curves: type of therapy

Re-entry patients (n=4,241), p<0.001

- Methadone maintenance
- Therapeutic community
- Abstinence oriented therapies
Concurrent psychotherapy (n=5,457), p<0.001

Provided to
- 7.6% of patients receiving methadone
- 4.9% of patients in TC
KM curves: dose of MM

Dose of MM (n=2,356), p<0.001

- 20-59 mg
- >= 60 mg
- < 20 mg
## Results of Cox model

<table>
<thead>
<tr>
<th>Determinants of treatment interruption</th>
<th>New patients (n=1,216)</th>
<th>Re-entry patients (n=4,241)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-66 years</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>25-29 years</td>
<td>1,02</td>
<td>0,84-1,24</td>
</tr>
<tr>
<td>18-24 years</td>
<td>1,15</td>
<td>0,95-1,38</td>
</tr>
<tr>
<td><strong>living condition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with own family</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Alone, with friends, homeless</td>
<td>1,37</td>
<td>1,09-1,73</td>
</tr>
<tr>
<td><strong>dual diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>yes</td>
<td>1,50</td>
<td>1,17-1,94</td>
</tr>
<tr>
<td><strong>use of cocaine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>yes</td>
<td>1,22</td>
<td>1,03-1,45</td>
</tr>
</tbody>
</table>
### Results of Cox model

<table>
<thead>
<tr>
<th>Determinants of treatment interruption</th>
<th>New patients (n=1,216)</th>
<th>Re-entry patients (n=4,241)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM &gt;= 60 mg die</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>MM 20-59 mg die</td>
<td>1,43</td>
<td>0,95-2,17</td>
</tr>
<tr>
<td>MM &lt;20 mg die</td>
<td>3,22</td>
<td>1,94-5,34</td>
</tr>
<tr>
<td>CT</td>
<td>0,88</td>
<td>0,51-1,51</td>
</tr>
<tr>
<td>Abstinence oriented therapies</td>
<td>3,68</td>
<td>2,46-5,50</td>
</tr>
<tr>
<td>Concurrent psycho-social treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>no</td>
<td>1,93</td>
<td>1,64-2,26</td>
</tr>
<tr>
<td>Concurrent psychotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>no</td>
<td>2,03</td>
<td>1,57-2,63</td>
</tr>
</tbody>
</table>
Gender differences

In both genders methadone maintenance followed by detoxification is the most frequent therapy.

Women seem to be:

- more willing to undertake psychosocial treatments and psychotherapy
- more able to agree on the conclusion of treatment
Gender differences in treatments

MM retention in treatment

HR=0.71, p=0.015

women (n=257)

men (n=1727)
Gender differences in treatments

CT retention in treatment

HR=1.28, p=0.128

men (n=433)

women (n=81)
Mortality in the cohort

At 18 months after the enrollment:

- 100 subjects were died
  - 37 under treatment
  - 63 out of treatment

- 41 deaths were caused by overdose
  - 10 under treatment
  - 31 out of treatment
## Causes of death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Deaths under treatment</th>
<th>Deaths out of treatment</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=37</td>
<td>N=63</td>
<td>N= 100</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>10 27.0</td>
<td>31 49.2</td>
<td>41</td>
</tr>
<tr>
<td>AIDS</td>
<td>13 35.1</td>
<td>6  9.5</td>
<td>19</td>
</tr>
<tr>
<td>Violent causes</td>
<td>4  10.8</td>
<td>13 20.6</td>
<td>17</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>3  8.1</td>
<td>3  4.8</td>
<td>6</td>
</tr>
<tr>
<td>Tumors</td>
<td>2  5.4</td>
<td>2  3.2</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system diseases</td>
<td>- -</td>
<td>1  1.6</td>
<td>1</td>
</tr>
<tr>
<td>Circulatory system diseases</td>
<td>1  2.7</td>
<td>2  3.2</td>
<td>3</td>
</tr>
<tr>
<td>Digestive system diseases</td>
<td>- -</td>
<td>3  4.8</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>4  10.8</td>
<td>2  3.2</td>
<td>6</td>
</tr>
</tbody>
</table>
### Protective value of treatment

<table>
<thead>
<tr>
<th></th>
<th>N overdose</th>
<th>Person-years</th>
<th>Rate $\times 1000$ p-y</th>
<th>HR crude</th>
<th>HR adjusted*</th>
<th>95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out of treatment</td>
<td>31</td>
<td>2913.8</td>
<td><strong>10.64</strong></td>
<td>1.00</td>
<td><strong>1.00</strong></td>
<td>-</td>
</tr>
<tr>
<td>In treatment</td>
<td>10</td>
<td>10207.7</td>
<td><strong>0.98</strong></td>
<td>0.09</td>
<td><strong>0.09</strong></td>
<td>0.04 - 0.19</td>
</tr>
</tbody>
</table>

**In treatment**

- **Methadone maintenance**
  - N: 7
  - Person-years: 5751.3
  - Rate $\times 1000$ p-y: **1.22**
  - HR crude: 0.11
  - HR adjusted*: 0.10
  - 95% IC: 0.04 - 0.24

- **Therapeutic community**
  - N: 0
  - Person-years: 1188.9
  - Rate $\times 1000$ p-y: -
  - HR crude: -
  - HR adjusted*: -
  - 95% IC: -

- **Tapering methadone**
  - N: 1
  - Person-years: 1495.7
  - Rate $\times 1000$ p-y: **0.67**
  - HR crude: 0.06
  - HR adjusted*: 0.07
  - 95% IC: 0.01 - 0.50

- **Other pharmacological**
  - N: 1
  - Person-years: 422.6
  - Rate $\times 1000$ p-y: **2.37**
  - HR crude: 0.22
  - HR adjusted*: 0.37
  - 95% IC: 0.05 - 2.76

- **Psychosocial**
  - N: 1
  - Person-years: 1349.2
  - Rate $\times 1000$ p-y: **0.74**
  - HR crude: 0.07
  - HR adjusted*: 0.07
  - 95% IC: 0.01 - 0.55

*Adjusted for age, gender, psychiatric comorbidity, HIV+, not-fatal overdoses, route of administration, length of heroin dependence
## Relation risk/last treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N° overdose</th>
<th>Person-years</th>
<th>Rate X 1000 p-y</th>
<th>HR crude</th>
<th>HR adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In treatment</td>
<td>10</td>
<td>10207.7</td>
<td>0.98</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Out of treatment</td>
<td>31</td>
<td>2913.8</td>
<td>10.64</td>
<td>10.86</td>
<td>11.11</td>
</tr>
</tbody>
</table>

### Out of treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N° overdose</th>
<th>Person-years</th>
<th>Rate X 1000 p-y</th>
<th>HR crude</th>
<th>HR adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone maintenance</td>
<td>9</td>
<td>997.7</td>
<td>9.02</td>
<td>9.21</td>
<td>8.26</td>
</tr>
<tr>
<td>Therapeutic community</td>
<td>5</td>
<td>231.7</td>
<td>21.58</td>
<td>22.02</td>
<td>23.00</td>
</tr>
<tr>
<td>Tapering methadone</td>
<td>7</td>
<td>814.1</td>
<td>8.60</td>
<td>8.78</td>
<td>9.35</td>
</tr>
<tr>
<td>Other pharmacological</td>
<td>7</td>
<td>612.2</td>
<td>11.43</td>
<td>11.67</td>
<td>12.09</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>3</td>
<td>250.5</td>
<td>11.98</td>
<td>12.23</td>
<td>22.31</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, psychiatric comorbidity, HIV+, not-fatal overdoses, route of administration, length of heroin dependence.
# Relation risk/time

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th>Person-years</th>
<th>Rate x1000 p-y</th>
<th>HR crude</th>
<th>HR adjusted*</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>In treatment</td>
<td>10</td>
<td>10207.7</td>
<td>0.98</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Out of treatment</td>
<td>31</td>
<td>2913.8</td>
<td>10.64</td>
<td>10.86</td>
<td>11.11</td>
<td>5.29 - 23.35</td>
</tr>
</tbody>
</table>

**Time from interruption of treatment (days)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Deaths</th>
<th>Person-years</th>
<th>Rate x1000 p-y</th>
<th>HR crude</th>
<th>HR adjusted*</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=30</td>
<td>13</td>
<td>561.4</td>
<td>23.15</td>
<td>23.64</td>
<td>26.57</td>
<td>11.56 - 61.10</td>
</tr>
<tr>
<td>31 - 60</td>
<td>4</td>
<td>388.8</td>
<td>10.29</td>
<td>10.50</td>
<td>12.87</td>
<td>4.00 - 41.41</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>14</td>
<td>1963.6</td>
<td>7.13</td>
<td>7.28</td>
<td>6.40</td>
<td>2.76 - 14.82</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, psychiatric comorbidity, HIV+, not-fatal overdoses, route of administration, length of heroin dependence*
## Mortality excess

Overall mortality excess versus general population

<table>
<thead>
<tr>
<th></th>
<th>Person-years</th>
<th>Deaths expected</th>
<th>Deaths observed</th>
<th>SMR</th>
<th>CL 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>under treatment</td>
<td>10207.72</td>
<td>9.40</td>
<td>37</td>
<td>3.93</td>
<td>2.85-5.43</td>
</tr>
<tr>
<td>out of treatment</td>
<td>2913.79</td>
<td>2.94</td>
<td>63</td>
<td>21.43</td>
<td>16.72-27.40</td>
</tr>
</tbody>
</table>
Active follow-up of a sample of the VEdeTTE 1 cohort, at least two years after the enrollment in the cohort

Objectives
To evaluate the effectiveness of treatments as regards:
- long-term legal and illegal drugs use
- overdose episodes
- family and social re-integration
- HIV, HBV and HCV morbidity
VEdeTTE 2

- Patients involved: 1,590
  - Acceptances 1126 (70.8%)
  - Refusals 222 (14.0%)
  - Not contacted 227 (14.3%)
  - Died and not replaced 15 (0.9%)
- Biological samples (hairs) collected: 984 (61.9%)
There is still a need of improvement of treatments based on the evidences

- MMT treatments are provided in a proportion of cases quite low if considering the evidences
- MMT treatments are provided at “ineffective” doses
- AOT are the most used treatments with new patients, with the risk of increasing their probability of drop-out
- also the association with psychotherapy could be improved

Recommendations (I)
treatment protects from OVD death
all treatments are protective
the 30 days after treatment interruption are at highest risk of death

from the mortality data, treatment retention is confirmed to be a good proxy of treatment effectiveness

Recommendation to practitioners: improving treatment retention..
Gender differences do exist as regards:
- risk factors
- substance use
- treatment adherence

In planning treatment strategies take into account:
- gender specific needs
- higher compliance of women with psychosocial treatments and psychoterapy
- differences in risk of interrupting treatments
From a cohort study

Evaluation of treatments as regards

- proportion of evidence-based treatments
- associations of treatments
- appropriatessness
- treatment retention
- mortality
- other outcomes (follow-up)
- gender differences
- ....

We can

1. study cause-effect relationships
2. improve quality of care