Heroin Addiction and Related Clinical Problems

the official journal of

Europad
European Opiate Addiction Treatment Association
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The vision
EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The Association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide.

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The 6th Europad Meeting took place, as scheduled, from October 31st to November 3rd in Paris. Plenty of effort was spent on organizing a meaningful event to represent all the different fields of interest that centre opiate addiction. In fact, the congress was planned as an opportunity to update and discuss a variety of clinical and therapeutic issues, acting on the concept that underlies Europad’s official magazine, *Heroin Addiction and Related Clinical Problems*.

Several non-European speakers contributed to the event, so documenting the growing tendency towards acknowledgment of the work being done in one country by those in other countries. Such cooperation will, hopefully, lead to a greater degree of uniformity in treatment methods between nations, in the light of a growing body of scientific knowledge which can be shared and agreed upon regardless of environmental differences. Beyond the usefulness of updating and improving skills, we are convinced that it is crucial that there should be a scientific community able to influence the health policies of single countries on the basis of opinions shared worldwide. Some kind of scientific brotherhood may also facilitate the funding or enhancement of cooperation between countries on world health and social well-being.

Some key lectures were intended to provide a summary and synoptic presentation of updated knowledge: in fact, later data and new approaches to drug addiction treatment, apart from proving effective in themselves, need to find their place after a comparison with older instruments. As safe, effective treatments are available for heroin addiction, the optimization of outcome and treatment-patient matching are the upcoming issues, rather than the question of which newer therapies may replace which older ones. One idea was that of suggesting a hierarchical system for the employment of various resources and a rationale for screening patients to ensure that the best available option is chosen.

Buprenorphine was extensively overviewed, from pharmacological grounds to clinical experiences. Its unique pharmacological profile has lately been of great interest in testing and exploring the relationship between opiate function modulation and behavioural correlates. Apart from the basic issues of effectiveness, safety and suitability for different categories of drug addicts, there has been increasing interest in its psychotropic properties and the therapeutic potential of non-mu opioid modulation.

Methadone treatment was an object of advanced discussion, around issues of long-term safety and dose adequacy. The usefulness of higher-dose methadone on patterns of polyabuse or switching abuse from blocked or unavailable opiates to cross-reacting substances was also pointed out. Data gathered during longest-term methadone maintenance treatment programmes were presented, as a means of assessing of what limitations on global adjustment still persist. We would like to remark how the adoption of effective treatment for drug addiction made it possible to deal with problems shared by addicts and non-addicted people, such as quality of life.

Harm reduction techniques and strategies were updated in a dedicated section. We hope that a clearer concept was provided about what role harm reduction should play.
with respect to other treatment approaches. In fact, it is our duty to stress the priority to be given to enrolling patients in effective treatment programmes, rather than letting low-threshold but non-therapeutic interventions fill the vacuum left by treatment omission or malpractice. On the other hand, harm reduction should be developed in order to increase entrance rates of street addicts into treatment programmes, through earlier phases of prevention and motivation enhancement.

Dual diagnosis was a hot subject for discussion, given the lack of uniformity between diagnostic trends across countries. Experiences with chronic psychosis and bipolar disorder were presented with a comparative intent. Moreover, a look was taken into the psychotropic properties of opioids, suggesting that anti-craving agents may offer an additional useful approach to countering the psychiatric syndromes of addicts at higher dosages, and possibly to helping the non-addicted mentally ill, too.

The therapeutic relationship between treatment staff and patients is a crucial issue in contexts where treatment features are applied in an adequate way. In such conditions, motivation development and orientation carry great weight in determining whether treatment is applied for and whether retention rates increase. Plenty of time was therefore dedicated to motivation interventions, such as the psychotherapy of choice in the integrated treatment of heroin addicts.

Looking forward, our hope is that future meetings will provide participants with a similar level and variety of acknowledgements, and that political authorities will show increasing interest in learning and applying what is shared and agreed upon by our scientific community. We also hope that the press will continue to help us provide heroin-related science with a viable channel of information for public opinion to become aware of the state-of-the art in this field.

Icro Maremmani

President

Pisa, January 2005
Buprenorphine induction and stabilisation
in the treatment of opiate dependence

Christopher Doran 1, Jeremy Holmes 2, Dieter Ladewig 3
and Walter Ling 4

Summary

Many early trials of buprenorphine in opiate dependence used fixed doses and slow induction protocols. However, more recent data show that subjects requiring higher doses need to be stabilised more rapidly. Analysis of ten trials suggests a relationship between days taken to reach a 6 mg buprenorphine tablet equivalent dose and retention of subjects at 4 weeks. Recent US studies show that dosage can be stepped up quickly, e.g. 8 mg on Day 1, 16 mg on Day 2. Maintenance dosage should then be adjusted to meet patients’ clinical needs; fixed dose studies ignore the breadth of buprenorphine’s effective dose range.

Key Words: Buprenorphine - Methadone - Opiate Dependence - Induction - Dosing

Introduction

Evidence on the use of buprenorphine in the treatment of opiate dependence is the subject of increasing debate amongst both physicians and policy-makers.

The introduction of a new medication in the context of existing therapeutic approaches, in this case predominantly methadone, naturally leads to caution regarding change. This paper summarises what is known regarding induction with buprenorphine as compared to methadone, and the associated outcomes in terms of stabilisation and maintenance.
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It discusses the findings and implications of three recent meta-analyses, and reviews the underlying trial evidence. In particular, we have explored the relationship between speed of induction and rates of retention in treatment.

**Meta-analyses**

West et al \(^{(40)}\) analysed data from nine trials comparing buprenorphine with methadone using urinalysis as the common outcome measure. The results indicated a non-significant superiority for methadone. However, the heterogeneity in effect sizes led to a focused test being undertaken on four studies that provided data on subjects’ previous experience with methadone maintenance programmes. This gave a significant result \((p<0.01)\) in favour of buprenorphine’s efficacy in preventing illicit opiate usage.

West et al \(^{(40)}\) comment that “for all practical purposes” buprenorphine and methadone can be used with equal success, but that there are other aspects that may influence clinicians’ choice of treatment. These include the superior safety profile of buprenorphine and its milder withdrawal syndrome. The authors also comment on the high degree of variability in the findings of individual studies.

Barnett et al \(^{(4)}\) compared data from five randomised clinical trials of maintenance treatment, i.e. the use of buprenorphine as a substitute for heroin, with retention in treatment as the primary outcome measure. Reduction in opiate use was also measured by means of urinalysis.

Barnett et al \(^{(4)}\) found that, for retention in treatment and urinalysis, 8-12 mg/day buprenorphine was superior to 20-35 mg/day methadone but not as effective as 50-80 mg/day methadone. However, they also found that the differences in effectiveness were small by comparison with the wide variation in outcomes achieved in different treatment programmes.

They concluded that the observed difference in effect between the two treatments might be attributable to the dose used and to other features of study design. In particular, in the three fixed dose studies which found methadone to be more effective than buprenorphine \(^{(32)(18)(19)}\) all the authors suggested that higher doses of buprenorphine may have been needed.

The third recent meta-analysis, by Farre et al \(^{(11)}\), focused primarily on methadone studies but included the same five buprenorphine studies as Barnett et al \(^{(4)}\) plus one additional study by Strain et al \(^{(34)}\).

Farrel et al \(^{(11)}\) classified maintenance doses of buprenorphine of >8mg per day as “high dosage”, and found a non-significant difference between this and high dose methadone in terms of both positive urines and retention in treatment. Their data indicate that both methadone and buprenorphine show a dose-response relationship. They also conclude that buprenorphine has certain other advantages over methadone, including alternate day dosing, the possibility of less social stigma, only mild withdrawal symptoms following abrupt discontinuation and a theoretically lower risk of overdose.

The focus of all three meta-analyses was on relatively early studies of buprenorphine
in which the drug was fitted to the known optimal conditions for methadone induction, at a time when the optimal conditions for buprenorphine were unknown. By contrast, current treatment guidelines such as the Australian National Clinical Guidelines (23) www.health.gov.au) provide for a much more rapid rate of induction of buprenorphine.

For those involved in running treatment programmes outside the conditions of a clinical trial it is important to recognise that dosing schedules for buprenorphine have changed from those used in the early trials as more experience with the drug has been generated and the implications of its different pharmacology have become better understood.

**Treatment Induction and Dosing Studies**

The phenomenon of matching the buprenorphine induction protocol to that for methadone in clinical trials stems from the traditional concerns regarding safety in the treatment of opioid addiction. In particular, the well-established evidence that increasing the dose of methadone too quickly can lead to fatalities (6)(17)(38)(41) has understandably encouraged a cautious approach.

To the present authors’ knowledge, there have been no fatalities reported during induction onto buprenorphine. Unlike methadone, buprenorphine is a partial agonist at the mu-opiate receptor, and there is consequently a ceiling on its ability to cause respiratory depression. The agonist effect of buprenorphine has been studied at sublingual doses of 2-32 mg and intravenous doses of 2-16 mg in non-dependent individuals and a plateau reached in both cases which is below the threshold for potentially fatal respiratory depression (39)(37).

There is other strong evidence of buprenorphine’s safety (20)(30) including its superiority over methadone in overdose (3). In dosing regimen studies, patients have received up to four times their normal daily dose without experiencing any additional opioid agonist effects compared to their daily dose (28).

There is now also compelling evidence that the step-up dosing in the induction phase can be much more rapid with buprenorphine than with the traditional five to seven day or longer protocol (depending on final dose) used with methadone (14)(16). In a one-year US clinical trial, 472 heroin subjects safely received 8 mg buprenorphine on the first day of the induction protocol and then proceeded to a dose of 16 mg on Day 2 (13). In the open label flexible dosing phase of this study, the dose could be adjusted up to 24 mg per day, depending on the needs of the patient. This induction schedule is in marked contrast to those used in many studies in the EU, such as that reported by Pani et al (26) in which it took 7 days to reach a dose of 8 mg of buprenorphine.

The safety issues associated with rapid induction of buprenorphine were considered by Di Petta et al (8) in a recent study of 650 subjects in Italy. Subjects transferred from heroin were induced with 32 mg buprenorphine on Day 1, this dosage remaining constant over the first five days. Patients transferred from methadone were induced with doses reaching 32 mg (for the lowest dose methadone subjects) to 24-56 mg (for
Table 1: Dosage Regimes in Selected Trials of Buprenorphine Induction and Maintenance

<table>
<thead>
<tr>
<th>Trial</th>
<th>Buprenorphine Induction Schedule</th>
<th>Buprenorphine Maintenance Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies included in Barnett et al (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Johnson et al (15)</td>
<td>3 mg, 6 mg and 11 mg on Days 1, 2 and 3</td>
<td>11 mg fixed dose from Day 3 to the end of Week 17</td>
</tr>
<tr>
<td>*Kosten et al (18)</td>
<td>3 mg on Day 1 and gradually increased to 9 mg during the first 2 weeks</td>
<td>3 or 9 mg fixed dose for 24 weeks</td>
</tr>
<tr>
<td>*Strain et al (34)</td>
<td>3 mg, 6 mg, 9 mg and 11 mg on Days 1, 2, 3 and 4</td>
<td>11 mg fixed dose for 3 weeks, then flexible dosing up to 23 mg to the end of Week 16</td>
</tr>
<tr>
<td>*Ling et al (19)</td>
<td>3 mg, 6 mg and 11 mg on Days 1, 2 and 3</td>
<td>11 mg fixed dose from Day 3 to Week 52</td>
</tr>
<tr>
<td>*Schottenfeld et al (33)</td>
<td>1 mg, 3 mg and 6 mg or 6 mg, 11 mg and 17 mg on Days 1, 2 and 3</td>
<td>6 or 17 mg fixed dose from Day 15 to the end of Week 24</td>
</tr>
<tr>
<td>Additional studies included in West et al (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eder et al (10) – (interim data) superseded by Fischer et al (12) – (full data)</td>
<td>2 mg, 4 mg, 6 mg and 8 mg on Days 1, 2, 3 and 4</td>
<td>Individual stable doses determined during induction maintained for 24 weeks</td>
</tr>
<tr>
<td>Uehlinger et al (36) superseded by Petitjean et al (27)</td>
<td>4 mg on Days 1-3. Flexible dose titration from Day 4 to 8 mg on Day 4, up to 12 mg by Day 8, and up to 16 mg by Day 15</td>
<td>Individual stable doses determined during induction maintained during Days 22-42</td>
</tr>
<tr>
<td>Additional study included in Farre et al (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Strain et al (35)</td>
<td>3 mg, 6 mg, 9 mg and 11 mg on Days 1, 2, 3 and 4</td>
<td>11 mg fixed dose for 3 weeks, then flexible dosing up to 23 mg to the end of Week 16</td>
</tr>
<tr>
<td>Other studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Ling et al (20)</td>
<td>3 mg, 6 mg, 11 mg, 17 mg and 23 mg on Days 1, 2, 3, 4 and 5 (according to randomised fixed dose group). 2 mg control group received this dose throughout the study</td>
<td>1 mg, 6 mg, 11 mg and 23 mg fixed doses from end of induction to end of Week 16</td>
</tr>
<tr>
<td>Ling et al (21)</td>
<td>8 mg, 12 mg, 16 mg and 24 mg on Days 1, 2, 3 and 4</td>
<td>Open flexible dosing of up to 24 mg tablet</td>
</tr>
</tbody>
</table>
C Doran et al.: Buprenorphine induction and stabilisation in the treatment of opiate dependence

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage Schedule</th>
<th>Induction Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pani et al (26)</td>
<td>2 mg, 2 mg, 4 mg, 4 mg, 6 mg, 6 mg, 8 mg and 8 mg on Days 1-8</td>
<td>8 mg fixed dose for 6 months</td>
</tr>
<tr>
<td>*Johnson et al (16)</td>
<td>6 mg on Day 1, increasing to 11 mg on Days 2 through 7</td>
<td>Flexible dosing up to 46 mg (32 mg solution)</td>
</tr>
<tr>
<td>Fudala et al (13)</td>
<td>8 mg on Day 1, 16 mg on Day 2</td>
<td>4-week double blind phase: 16 mg or placebo tablet. 48 week open safety phase: flexible dosing of 4 mg - 24 mg tablet</td>
</tr>
<tr>
<td>Mattick et al (24)</td>
<td>Ave 3.9 mg, 4.3 mg, 4.5 mg, 5.4 mg on Days 1, 2, 3 and 4 rising to ave 6.7 mg on Day 7, 8.6 mg on Day 14</td>
<td>Open flexible dosing</td>
</tr>
</tbody>
</table>

* These studies conducted with buprenorphine sublingual solution; tablet equivalent dosages presented are based on 70% bioavailability vs solution, using conversion factor of 1.43, rounded to nearest 1mg

the highest dose methadone subjects) by Day 5. No significant side effects relating to respiratory function, or liver or kidney function, were identified.

Table 1 summarises buprenorphine tablet-equivalent dosage schedules in each of the clinical studies included in the meta-analyses by Barnett et al (4), West et al (40) and Farre et al (11). Tablet-equivalent doses have been used for consistency, based on a bioavailability of 70% compared to the solution formulation (5×25)(22). This relative bioavailability is accepted by the US Food & Drug Administration for product labelling purposes on Subutex ® tablets.

It should be noted that the paper by Eder et al (10) reported interim data and was superseded by Fischer et al (12), and the paper by Uehlinger et al (36) was in some respects superseded by that by Petitjean et al (27).

Six additional studies (20)(21)(26)(16)(13)(24) are also included in Table 1 for comparison. These indicate the growing body of evidence regarding more rapid rates of induction than those considered in the meta-analyses.

Figure 1 shows the relationship between speed of induction onto 4 mg per day buprenorphine solution or 6 mg per day buprenorphine tablet (Subutex®) and subject retention at 4 weeks (correlation coefficient -0.815). The figure has been compiled from published studies in which these data were presented or have been made available to the present authors. It therefore does not provide comprehensive data across all the studies cited in Table 1. Nevertheless, the available data suggest that more patients will drop out from treatment the longer the period taken for induction onto buprenorphine.

A 4 mg dose of buprenorphine solution (approximately 6 mg tablet equivalent) is recognised as one that will hold patients in treatment. In particular, this was demonstrated in the study by Schottenfeld et al (32) in which 94% of subjects in the 12 mg...
buprenorphine group remained in treatment after 4 weeks; these patients received 4 mg solution per day for Days 1-7.

The study reported by Ling et al (20) was a large scale double-blind trial in the USA of four different dosage groups receiving buprenorphine. The group following the most rapid induction protocol to achieve the highest dose of 16 mg solution comprised 181 subjects who received 2 mg on Day 1, 4 mg on Day 2, 8 mg on Day 3, 12 mg on Day 4 and 16 mg on Day 5. Of these subjects, 110 (61%) completed the full 16 week protocol, compared to 52% and 51% completion rates for the 8 mg and 4 mg groups respectively. There were no deaths in any of the study groups and none of the adverse medical events reported were found to be dose-related.

Although the induction schedules reported in the two studies by Ling et al (20, 21) cited in Table 1 are rapid in comparison to the early EU studies, they are relatively slow in comparison to that used by Fudala et al (13) and the now accepted faster induction options in use in Australia which provide for dosage of up to 24 mg per day by Day3 (23) and www.health.gov.au). There is thus mounting evidence of the benefits of more rapid induction with buprenorphine.

Restraining the induction protocol for buprenorphine to match the relatively slow protocol for methadone, and focussing on fixed maintenance dose studies, risks a bias in comparative trials that favours methadone. This fact has been commented on in some of the study reports and needs to be appreciated when trial results are being reviewed by decision-makers in drug addiction programmes.

Figure 1. Induction Rate versus % Retention at 4 Weeks
Stabilisation & Maintenance Studies

Because of the comparison problems associated with matching a buprenorphine to a methadone induction protocol, buprenorphine’s effectiveness in the stabilisation and maintenance phase needs to be considered separately from that in the induction phase.

A good example of where this is necessary in interpreting the trial data is the study reported by Mattick et al (24). The rate of induction onto buprenorphine in this study was matched to the slower rate of methadone induction, resulting in more buprenorphine subjects dropping out early in the trial. However, this was a flexible dose study in which the dose of buprenorphine tablet (Subutex®) or methadone was titrated to the clinical needs of the subject, and amongst those who received adequate daily doses of either drug at around 10 days and remained in the trial, there were no differences in rates of retention in treatment following stabilisation.

Mattick et al (24) also found that, in the first 6 weeks (including induction) there were no differences between buprenorphine and methadone with regard to reductions in opioid use, measured by urine toxicology, or heroin craving, measured on a visual analogue scale.

A key finding was that the effective dose range of buprenorphine was quite broad with some subjects being adequately maintained on 4 mg (tablet) per day while others required up to 24 mg per day. The mean daily dose was 10.9 mg/day at end of Week 6.

In the second part of this study, during a 7 week period where alternate day dosing of buprenorphine was compared with daily methadone administration, the effectiveness of buprenorphine was maintained with no differences in the percentages of opiate-free urines or retention in treatment compared to the methadone group. The mean equivalent daily dose of buprenorphine during this alternate day dosing period was comparatively stable, ranging from 10.8 to 11.2 mg per day.

Similarly, Petitjean et al (27), in a double-blind flexible dosing study conducted in Switzerland comparing buprenorphine with methadone, found the mean stabilisation dose of buprenorphine to be 10.5 mg at six weeks. Comparable reductions were reported in opioid-positive urines (p=0.759) and heroin craving (p=0.735) for buprenorphine and methadone.

A number of published studies have reported that the efficacy of buprenorphine is not compromised when buprenorphine is dosed on alternate days with double the established daily dose, or three times a week, with double, double and three times the established daily dose, respectively (1)(7)(2)(33). Johnson et al (16) found that three times per week dosing of buprenorphine was equivalent to high dose methadone, and both regimes were superior to low dose methadone.

Petry et al (28) found that, in a comparison of four different buprenorphine dosing regimes, 86% of subjects preferred double-every-other day or triple-every-third day dosing to daily dosing; retention in treatment and urinalysis were not compromised in these less than daily dosing schedules. Importantly, there were no increased agonist
effects or adverse events when dosing at up to four times the 8 mg daily dose (i.e. 32 mg, which is the maximum daily dose supported by the current safety data).

Less than daily dosing of buprenorphine is of significant benefit in countries or clinics where supervised dosing is mandatory - and therefore has an obvious cost benefit in favour of buprenorphine compared with daily methadone. Doran et al \(^{(9)}\) argued that the possibility of thrice weekly dosing with buprenorphine would be likely to reduce the small cost difference between buprenorphine maintenance and methadone maintenance which arises from the time taken for supervised dosing.

**Conclusions**

Randomised trials comparing methadone and buprenorphine should be viewed as comparisons between a medication which is widely used and understood, and a newer therapy which has had understandable restrictions placed on it in its early days.

Comparisons undertaken to date have compared the well-known “gold standard” usage of methadone with early experimental and cautious buprenorphine dosing schedules. However, a slow induction with buprenorphine will tend to lead to inadequate dosing in the first days of treatment and a higher early drop-out rate than would be the case with a more rapid induction protocol.

Moreover, the use of fixed doses in trials does not reflect clinical reality, in which each patient is titrated to a dose that is clinically right for that individual. Data from flexible dosing studies such as that reported by Mattick et al \(^{(24)}\) show that, in practice, the dosage needs of different patients in order to achieve stabilisation are very varied. This is ignored by trials using fixed dose regimes.

For the introduction of buprenorphine into treatment programmes, rapid induction and attainment of a maintenance dose, for example with dose increments of 4 mg to 8 mg per day, should be considered. Once patients are stabilised on buprenorphine, the evidence suggests that effectiveness is comparable between buprenorphine and methadone \(^{(27)(24)}\). However, with buprenorphine the risk associated with overdosing appears to be greatly reduced. In addition, buprenorphine offers the flexibility of dosing three times a week, every other day or every third day. These schedules are often preferred by patients over daily dosing and do not compromise rates of retention in treatment \(^{(29)}\).

In the flexible dosing studies conducted to date, there is a close similarity in terms of mean maintenance doses of buprenorphine tablet; 10.5 mg in Switzerland \(^{(27)}\), 10.9 mg and 10.8-11.2 mg in Australia \(^{(36)(24)}\) and approximately 11-12 mg tablet equivalent in the USA \(^{(34)}\).

These mean dosages underline the point that a fixed or maximum dose of 8 mg or less (11 mg tablet equivalent), as used in four of the five studies analysed by Barnett et al \(^{(4)}\) and four of the six studies analysed by Farre et al \(^{(11)}\), is likely to lead to a number of patients being under-dosed, with a negative impact on retention in treatment.

The other meta-analysis reported by West et al \(^{(40)}\) concluded that for practical purposes
buprenorphine and methadone are equally effective, but that buprenorphine’s superior safety profile and milder withdrawal effects might influence the choice of treatment.

The limitations of the present review include the fact that comprehensive data to compare induction rates with retention in treatment across all the studies included in the three meta-analyses were not available to this review’s authors. Other differences between the studies such as levels of counselling, subjects’ prior methadone experience and other drug use, might also have influenced the results. Nevertheless, the findings are indicative of an important issue.

A key area for further research is therefore to establish a true comparison of methadone induction (over 7-14 days) with buprenorphine (over 2-4 days) in terms of both efficacy and safety. This has to be integrated with the already available evidence on maintenance before any robust conclusions can be drawn regarding the overall effectiveness and cost-effectiveness of buprenorphine in routine practice.

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Clinical significance of electroencephalographic abnormalities in heroin addicts: systematic review

Anna G. Polunina, Dmitry M. Davydov and Evgeny A. Briun

Summary

The present review is the result of a systematic attempt to collect and analyze all the available contemporary data on neurological and psychophysiological aspects of EEG changes in heroin addicts. These data offer valuable objective insights into clinically significant encephalopathic and/or disintegrative processes in these patients. Thirteen computer EEG studies published since 1995 have been analyzed. It can be concluded that the sensitivity of computer EEGs to heroin-induced brain alterations is comparable with other contemporary neuroimaging techniques. In any case, precise recommendations for their use in regular medical practice must await further extensive research in this field.

Key Words: EEG - Heroin - Brain - Addiction - Electric activity

Introduction

Chronic heroin abuse induces significant changes in the central nervous system of human and animal individuals. Common consequences of chronic opioid consumption include addiction, tolerance to certain effects of the drug and the induction of dependence, with withdrawal symptoms after the discontinuation of drug administration. The weakening of ethical and moral attitudes, carelessness and self-centredness along with a loss of elementary self-preservation are other well-known symptoms of personality changes, which necessarily progress in each heroin addict. At present, the
neural mechanisms through which this “heroin encephalopathia” syndrome develops are incompletely understood. In their review of the neuropathology of heroin abuse, Büttner and colleagues \[10\] concluded that chronic heroin per se does not induce gross brain alterations. On the other hand, a set of abnormalities in receptor/second messenger systems was consistently demonstrated in the frontal and temporal cortex of chronic heroin addicts at several postmortem studies. Subcellular damage to frontal cortex neurons and astrocytes was also reported in these cohorts of patients \[19, 32\]. Animal studies confirmed opioids’ capacity to remodel the density of dendritic spines in many brain regions and so affect their synaptic input \[24, 31\]. Structural alterations in mesolimbic dopamine neurons were also found in the brains of rats treated chronically with morphine \[36\]. Hence, morphological studies consistently supply evidence that chronic opioid consumption induces characteristic brain alterations which probably underlie most psychopathological symptoms in this problematic patient population.

Seventy per cent of heroin addicts demonstrate prominent qualitative abnormalities in EEG recordings soon after heroin withdrawal \[9, 20, 25\]. The latter include marked EEG desynchronization, along with large amounts of low-amplitude “theta-delta” waves in central regions. During the first 3-6 months after complete withdrawal of the drug, many patients demonstrate dramatic normalization of brain electric activity \[9, 20\]. However, residual changes are still commonly observed. Some qualitative abnormalities in brain oscillations may be of clinical value. For instance, patients with paroxysmal/epileptiform bursts at frontocentral regions often take significantly lower intravenous dosages of heroin than patients with epileptiform activity in posterior brain regions \[29\]. The mechanisms of the latter phenomenon are unclear. It is likely that differences in epileptogenic and anticonvulsant cerebral opiate systems influence the course of drug abuse and other behaviours in heroin addicts.

Even a visual analysis of EEG recordings of heroin abusers may therefore give some information about the dynamics of withdrawal-related electrophysiological processes in the brain, or about individual abnormalities which may affect drug abuse behaviour. It is reasonable to expect that computer methods for analyzing electric activity in the brain may offer a range of new opportunities for elucidating the sources and clinical significance of EEG abnormalities in this patient population.

During the last decade, psychophysiology has made considerable advances in clarifying the functional role of rhythmic neuronal oscillations in cognitive processes \[5, 37\]. It has been shown that delta, theta, alpha, beta and gamma EEG frequency bands subserve various different cognitive processes. Slow (delta and theta) EEG oscillations indicate the involvement of widespread multineuronal networks in a cognitive operation, whereas faster (alpha, beta and gamma) frequency bands operate on more direct and/or localized interneuronal associations. Thus, deviations in EEG frequency distribution from normal values may provide an objective parameters for the disturbances in a certain type of cognitive process in a concrete individual.

In contrast to alcoholism or psychostimulating drug abuse, only a few quantitative studies have addressed spontaneous or elicited EEG abnormalities in chronic heroin users.
The aim of the present systematic review has been to collect and analyze all available contemporary data on neurological and psychophysiological aspects of EEG changes in heroin addicts, which might provide valuable objective information about clinically significant encephalopathic and/or disintegrative processes in these patients.

Methods

A preliminary search for the relevant publications was conducted using the Pubmed database with the following set of key words: “EEG AND (addiction OR dependence OR abuse) AND (heroin OR opioid OR morphine OR opiate)”. The main search was based upon appropriate references in relevant review or original articles. Publications were selected for the analysis if they fulfilled the following criteria: (1) original reports, (2) published since 1995, (3) pertinent to computer EEG studies on spontaneous or elicited electric activity in chronic heroin addicts without gross neurological or psychiatric deficits; and (4) reports that compared brain electric activity in heroin addicts with that of healthy controls. Thirteen appropriate publications by six research groups were found and included in the present systematic review. The features of the studies that have been analyzed are shown in Table 1.

Results

The techniques used for the registration and analysis of spontaneous and event-related brain electric activity differed in studies analyzed; this made direct comparisons impossible. Nevertheless, some consistent and similar findings were reported by different research groups and are presented here.

Most EEG parameters were, in fact, normal in heroin addicts 2-3 months after complete opioid withdrawal. These parameters included: (1) absolute spectral power in 5-8 frequency bands \[11, 17\], (2) relative spectral power \[11, 35\], (3) intrahemispheric and interhemispheric coherence in eight (excluding gamma) frequency bands \[17\], (4) amplitude of some types of elicited potentials \[6, 8, 16\], (5) latency of elicited brainstem auditory potentials \[2\], visual potentials \[6\] and P300 component of cognitive elicited potentials \[7, 27\].

Some of the parameters named above were abnormal in patient cohorts with a shorter length of abstinence. For instance, two studies showed a deficit in alpha2 power during the first weeks after heroin withdrawal, with a strong trend towards normalization in patients with a longer period of abstinence \[30, 35\]. An excess of beta2 activity was demonstrated in two heroin addict cohorts at the same interval after withdrawal \[17, 30\]. The rapid recovery of beta oscillations after a longer period of abstinence was observed in our patient population, too. Thus, prominent disturbances in absolute or relative spectral power are characteristic only for early heroin abstinence, and were no longer recorded after 2-3 months of opioid withdrawal. Most studies failed to find any significant differences in the amplitude and/or latency of short and intermediate
<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Patients</th>
<th>Mean age</th>
<th>Years of heroin use</th>
<th>Abstinence</th>
<th>Parameters analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shufman et al., 1996</td>
<td>1 Current addicts (n=20)</td>
<td>32.5</td>
<td>4.5</td>
<td>no</td>
<td>2 Ex-addicts (n=20) 33.0 3.5 &gt;2 weeks</td>
<td>Relative power at O1-Cz (resting EEG)</td>
</tr>
<tr>
<td></td>
<td>2 Ex-addicts (n=20)</td>
<td>33.0</td>
<td>3.5</td>
<td>&gt;2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costa &amp; Bauer, 1997</td>
<td>Ex-addicts (n=19)</td>
<td>31.7</td>
<td>–</td>
<td>2.9 months</td>
<td></td>
<td>Absolute and relative power at 9 midline leads (resting EEG)</td>
</tr>
<tr>
<td>Bauer, 1998</td>
<td>Ex-addicts (n=21)</td>
<td>33.2</td>
<td>10.6</td>
<td>3 months</td>
<td></td>
<td>Pattern shift visual elicited potentials (N75 and P100) at O1 and O2</td>
</tr>
<tr>
<td></td>
<td>2 Methadone-maintained, HIVnegative</td>
<td>40.1</td>
<td>17</td>
<td>no</td>
<td></td>
<td>Amplitude and latency of P300 component of cognitive potentials in 15 leads</td>
</tr>
<tr>
<td></td>
<td>3 Methadone-maintained, HIVpositive</td>
<td>41.8</td>
<td>23.8</td>
<td>no</td>
<td></td>
<td>Latency of elicited brainstem auditory potentials Amplitude and latency of P300</td>
</tr>
<tr>
<td>Bauer, 2001</td>
<td>Ex-addicts (n=29)</td>
<td>33.6</td>
<td>9.9</td>
<td>3 months</td>
<td></td>
<td>Latency of P600 component of cognitive potentials in 15 leads</td>
</tr>
<tr>
<td>Arzumanov et al., 2001</td>
<td>Addicts in detoxification (n=60)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td>Latency of elicited brainstem auditory potentials Amplitude and latency of P300</td>
</tr>
<tr>
<td>Papageorgiou et al., 2001</td>
<td>Ex-addicts (n=20)</td>
<td>31.1</td>
<td>9.0</td>
<td>&gt;6 months</td>
<td></td>
<td>Latency of P600 component of cognitive potentials in 15 leads</td>
</tr>
</tbody>
</table>
Table 1. Characteristics of the studies reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Patients</th>
<th>Mean age</th>
<th>Years of heroin use</th>
<th>Abstinence</th>
<th>Parameters analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al., 2002</td>
<td>Ex-addicts (n=29)</td>
<td>32.3</td>
<td>10.8</td>
<td>3.2 months</td>
<td></td>
<td>Amplitude of slow potentials (waveform between 500 and 950 ms) in 15 leads</td>
</tr>
<tr>
<td>Arzumanov et al., 2003</td>
<td>Ex-addicts (n=20)</td>
<td>18</td>
<td>0.5 - 3</td>
<td>&gt;2 weeks</td>
<td></td>
<td>Amplitude and latency of N200 and P300</td>
</tr>
<tr>
<td>Franken et al., 2003</td>
<td>Ex-addicts (n=19)</td>
<td>33.5</td>
<td>9.0</td>
<td>&gt;2 weeks</td>
<td></td>
<td>Amplitude of P3 and slower potentials at heroin-cued and neutral stimuli in 11 midline leads</td>
</tr>
<tr>
<td>Franken et al., 2004</td>
<td>Ex-addicts (n=18)</td>
<td>32.4</td>
<td>9.0</td>
<td>&gt;2 weeks</td>
<td></td>
<td>Absolute and relative power in 21 leads, intrahemispheric (Fp1/O1, Fp2/O2) and interhemispheric (F7/F8, T3/T4, T5/T6) coherence</td>
</tr>
<tr>
<td>Papageorgiou et al., 2004</td>
<td>Current addicts (n=20)</td>
<td>29.6</td>
<td>9.3</td>
<td>no</td>
<td></td>
<td>Amplitude and latency of P300 in 15 leads</td>
</tr>
<tr>
<td>Polunina &amp; Davydov, 2004</td>
<td>Addicts in detoxification (n=33)</td>
<td>21.7</td>
<td>1.5</td>
<td>6 - 141 days</td>
<td></td>
<td>Spectral power and mean frequencies in 19 leads (resting EEG)</td>
</tr>
<tr>
<td>Davydov &amp; Polunina, 2004</td>
<td>Addicts in detoxification (n=33)</td>
<td>21.7</td>
<td>1.5</td>
<td>6 - 141 days</td>
<td></td>
<td>Resting EEG spectral power and mean frequencies in 19 leads, along with cognitive tests</td>
</tr>
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</table>
latency elicited potentials several months after heroin withdrawal.

From a neurological point of view, it is important to determine what alterations in the central nervous system underlie poorly reversible psychopathological changes in opioid addicts. Hypothetically, these alterations might correlate with chronic heroin and remain stable over a long (several month) period of heroin abstinence. Many EEG parameters were studied in this respect, but only three of them significantly correlated with the duration of chronic heroin intake.

In our study of young heroin addicts (median age = 21.5 years) with relatively short duration of chronic heroin intake (median = 1.5 years), the mean frequency of alpha2 oscillations in frontal/central regions was significantly faster in addicts with a long history of drug abuse.

Franken et al. [16] studied heroin addicts with a relatively long history of drug abuse (mean = 9.0) and found a correlation between decreased beta1- and theta-coherence in lateral frontal regions (F7/F8) and chronic heroin duration. Unfortunately, the authors did not analyze coherence in frontal/medial or central derivations in this study.

Finally, Bauer [6] reported a significant correlation between the prolonged latency of the N75 component of visual event-related potentials and chronic heroin duration in methadone-maintained patients with an extremely long heroin abuse history (mean = 17-24 years). The same study did not register any deviation in this parameter in ex-addicts with a moderate heroin abuse duration (mean = 10.6 years).

The studies just cited, therefore, show that chronic heroin length affects brain electric activity, and two of these studies consistently reported adverse heroin effects on electric activity at frontal/central regions. However, the considerable differences in duration of drug abuse and in the EEG parameters used in three studies should be noted.

Six reports by four research groups consistently pointed to the lateralized dysfunction of cognitive processing in chronic heroin abusers (see Table 2). Two studies found a more marked slowing of cognitive elicited potential components in the right than in the left hemisphere in heroin addict cohorts [2, 26]. Significantly, this phenomenon was reported in right frontal/central derivations in heroin addicts 6 months after heroin withdrawal [26].

In our young patient cohort, we observed a significant association between the elevation of mean frequency in alpha2 oscillations in frontal/central regions and poor performance in the ‘Tower of London’ test (TLT is a cognitive test sensitive to prefrontal cortex dysfunction [34]) [30]. When chronic heroin length was entered as a covariate, the latter variable removed alpha2 frequency at the right central lead (C4) and did not affect the strongest independent predictor of cognitive performance – alpha2 mean frequency at the left central (C3) derivation. These findings indicated that chronic heroin intake affected performance on TLT through the induced imbalances in right hemisphere neuronal networks. At the same time, a subgroup of heroin addicts, which included some patients with a long and some with a relatively short heroin history (e.g. 6 months), gave an extremely poor TLT performance and had an extremely high alpha2 mean frequency at C3 lead.
Very interesting findings were reported by Franken et al. [16], who reported significantly higher amplitudes of slow potentials in heroin addicts elicited by heroin-cued pictures than in healthy controls. These potentials were significantly more pronounced at the left central (C3) lead than at the right central (C4) one. More importantly, those high amplitudes of slow potentials at C3 were significantly correlated both with addicts’ desire to use heroin and with the need for relief from their negative state, and only the latter correlation was significant at C4. The same authors reported a direct association

<table>
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<th>Table 2. Neurological and psychophysiological correlates of brain electric activity in heroin addicts</th>
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<td><strong>Chronic heroin length correlates</strong></td>
</tr>
<tr>
<td>1. Frontal interhemispheric coherence decrease in beta1 and theta frequency band [Franken et al., 2004].</td>
</tr>
<tr>
<td>2. Frontal/central increase of mean frequency of alpha2 activity [Polunina &amp; Davydov, 2004].</td>
</tr>
<tr>
<td><strong>Lateralized imbalances of cognitive processing in heroin addicts</strong></td>
</tr>
<tr>
<td>1. Delayed latency of cognitive elicited potentials, most prominent at right hemisphere [Arzumanov, 2001; Papageorgiou et al., 2001].</td>
</tr>
<tr>
<td>2. Disturbances of normal interhemispheric asymmetry of cognitive stimulus processing [Arzumanov et al., 2003].</td>
</tr>
<tr>
<td>3. Increased left intrahemispheric gamma coherence (Fp1/O1) [Franken et al., 2004].</td>
</tr>
<tr>
<td>4. Strong association between elevated alpha2 mean frequency at central derivations (C3, Cz, C4) and poor performance on Tower of London test (planning dysfunction). This association was independent of drug abuse history at C3 and Cz, and, in contrast, was mediated by chronic heroin length at C4 [Davydov &amp; Polunina, 2004].</td>
</tr>
<tr>
<td>5. Significantly higher amplitudes of slow positive waves in left central lead (C3) compared with right central lead (C4) at showing of heroin-cued pictures. The elevated amplitude of slow potentials at C3 and Cz significantly correlated with desire to use heroin, and at C3 and C4 with need to relieve negative states [Franken et al., 2003].</td>
</tr>
<tr>
<td><strong>Other clinically significant abnormalities and correlates of brain electric activity in heroin addicts</strong></td>
</tr>
<tr>
<td>1. Residual changes in elicited brain potentials in heroin addicts 6 months after complete withdrawal of opioids [Papageorgiou et al., 2001; Papageorgiou et al., 2004].</td>
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<tr>
<td>2. Correlation between decreased P300 amplitude and number of DSM-IIIR childhood conduct disorder criterion behaviours [Bauer, 2001].</td>
</tr>
<tr>
<td>3. Correlation between increased temporal (T3/T4) interhemispheric delta coherence and chronic heroin craving/obsessive heroin-related thoughts [Franken et al., 2004]. Correlation between increased alpha1 coherence at frontal (F7/F8) and beta2 at temporal derivations and chronic heroin craving/obsessive heroin-related thoughts, respectively [Franken et al., 2004].</td>
</tr>
</tbody>
</table>
between craving magnitude and increased coherence between frontal/temporal derivatives in several frequency bands [17].

Thus, persistent brain electric abnormalities in chronic heroin addicts predominate in frontal/central regions, with a consistent trend towards a more marked right hemisphere involvement. Electric activity in the left central region correlated with prominent psychopathological symptoms in two studies, but not with heroin abuse duration.

**Discussion**

The data in the EEG studies cited above on the predominant dysfunction of frontal/central regions in chronic heroin abusers are consistent with functional neuroimaging findings in heroin addict cohorts. Five studies reported a decrease in blood flow or metabolism changes in frontal lobes and/or the anterior cingulate cortex in methadone-maintained or abstinent (up to several years) heroin-dependent subjects [18, 21-23, 28]. Two studies showed a trend towards more severe blood flow changes in the right frontal lobe of heroin addicts [21, 28]. So, the sensitivity of computer EEGs to heroin-induced brain alterations seems to be at least comparable with other functional neuroimaging techniques (SPECT, PET, fMRI et al.), which are much more expensive than EEGs and are only rarely available in regular clinical practice. Given the importance of frontal and right hemisphere structures in behaviour regulation and emotional processing, the cited EEG and other neuroimaging technique data offer a plausible explanation for marked psychopathological changes contrasting with intact general intelligence in
chronic heroin users.

The correlations of EEG abnormalities with heroin history that were reported in three studies seem to reflect different stages of heroin-related brain damage and disintegration rather than the same neuromorphological phenomenon. The patients in our study \[^{30}\] were young and healthy. Many of them were involved in heroin abuse during the ‘heroin epidemic’ in Russia between 1995 and 2000, when heroin was cheap and contained few contaminants. The EEG parameter in our patients — alpha2 mean frequency — that was correlated with chronic heroin duration differed significantly from that of controls. The patients of Franken et al. \[^{17}\] were older and had used heroin for about 9 years. Even so, only patients with a longer duration of heroin history in that cohort demonstrated decreased beta1- and theta-coherence in lateral frontal regions. Lastly, in the study of Bauer \[^{6}\], a similar patient population with chronic heroin intake averaging 10.6 years showed no deviations from controls in the latency of visual potentials. Only patients with heroin abuse lasting 17-24 years showed this evidence of diffuse brain damage affecting visual pathways in occipital regions. Thus, further research is needed in order to determine the clinical significance of reported neurophysiological correlates of chronic heroin duration. At present, the elevation of the mean frequency of alpha2-activity in frontal/central regions (especially, at C4) seems to be the earliest and most reliable EEG sign of adverse chronic heroin effects.

Two studies consistently showed a prominent association between abnormal electric activity at the left central lead and psychological deviations in heroin addicts. Franken et al. \[^{16}\] found marked involvement of this region in the craving processes. Whereas, we observed a highly abnormal frequency of alpha2-activity at C3, which significantly interfered with patients’ performance on the Tower of London Test. Importantly, this last association did not correlate with chronic heroin effects.

Neuroimaging studies of opiate craving on viewing heroin cues also recorded the predominant activity of the left hemisphere midline neural network, which consisted of the left anterior cingulate cortex, the left insula and/or the left frontal/temporal cortex \[^{12, 33}\]. Interestingly, that effective performance on TLT is predominantly supported by left frontal structures and the left anterior cingulate cortex, too \[^{1, 15, 34}\]. It seems probable that a neural functional network in this region is excessively involved in craving processes in heroin addicts and is no longer able to subserve a set of goal-directed (planning) cognitive operations such as TLT tasks. The absence of any direct relationship between neurophysiological abnormality in this region and chronic heroin duration provide evidence that a subpopulation of heroin addicts is especially likely to decompensate soon after involvement in drug abuse. These subjects probably suffer from psychiatric comorbidity (e.g. disturbances in left hemisphere alpha oscillating networks were also displayed in attention-deficit/hyperactivity disorder \[^{4}\] or antisocial personality disorder \[^{14}\]).

The present review supports the case for further extensive research into the clinical significance of brain electric activity abnormalities in heroin addicts. Contemporary methods of computer analysis of EEG recordings offer good opportunities to objectively and quantitatively evaluate deviations in brain functioning in this problematic
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patient population. The sensitivity of computer EEGs to heroin-induced brain alterations is comparable with other functional neuroimaging techniques, which have the disadvantage of being much more expensive and cannot be used regularly in the assessment of heroin addicts. Resting EEG band mean frequency (especially, alpha2 mean frequency in frontal/central regions) or coherence seem to be the most valuable parameters, and are easy to obtain. Even so, precise recommendations for using EEGs in the clinical management of heroin addicts will become feasible only after further thorough research in this field.

References

A. Polunina et al.,: Clinical significance of electroencephalographic abnormalities in heroin addicts. Systematic review


Alcohol abuse in heroin addicts:
An unfolding metabolic destiny

Matteo Pacini ¹, Anna Mellini ¹,₂, Maria Luisa Attilia ²
Mauro Ceccanti ² and Icro Maremmani ¹

Summary

This paper deals with the issue of alcohol-abusing heroin addicts. On the basis of clinical and epidemiological findings, a view is presented which links the two kinds of abuse along a common metabolic pathway. Some data about the former history of opiate abuse in treatment-seeking alcoholics help to indicate which heroin-related features may influence the incidence and severity of alcohol abuse in heroin addicts. Observations point to alcohol abuse as one possible pathological outcome of the opioid metabolic impairment underlying heroin addiction. When alcohol is a surrogate for heroin, social adjustment improves, but the metabolic destiny does not change, and the medical outcome is worsened to some extent by the low chances of curing a possible actual alcoholism to come. Correctly handled agonist treatments are crucial in preventing that kind of negative outcome, whereas alcohol abuse as an opioid equivalent calls for greater attention, to allow adequate assessment of the effectiveness of treatment programmes for opiate addiction.

Key Words: Heroin Addiction - Alcoholism - Metabolic Disease - Agonist Treatment

On the heroin side: alcohol abuse by heroin addicts undergoing treatment

The available data agree in indicating that a history of alcohol abuse is quite common in addicts entering Methadone Maintenance Treatment Programmes (MMTPs), while the impact of MMTPs on pre-existing alcohol abuse is highly variable, in spite of a similar grade of effectiveness on heroin use. A sharp decrease has, in fact, been reported for some populations (⁴,⁵,⁹,²⁴), but post-treatment cases of severe alcohol abuse are possible, especially due to the exacerbation of pre-existing abuse liability (⁷, ²⁵). Moreover, the
possible increase in alcohol consumption during MMTPs develops along dwindling heroin use, suggesting a negative correlation between the two, at least in programmes employing lower dosages of methadone (1). In other cases, alcohol abuse appears to be positively correlated with polyabuse (6, 8, 26-29).

In the PISA-SIA Group experience, alcohol use is common among heroin addicts at treatment entrance, whatever treatment option is applied for. Its prevalence rate is 48.8% among subjects entering a MMTP, 35.5% among those applying for a Buprenorphine Maintenance Treatment Programme (BMTP) and, surprisingly, as high as 53.5% among addicts selected to start a Naltrexone Maintenance Treatment Programme (NMTP) (13). Rates are quite similar between MMTP and NMTP, for which latter different selection criteria are employed. Generic safety criteria are the only threshold for entry into the Pisa-MMTP, whereas subjects applying for a NMPT have to go through a baseline naloxone challenge to determine naltrexone administration feasibility. Thus, alcohol use is quite frequent among addicts who are not currently using heroin on a regular basis, so suggesting that opiate addicts may attempt to abstain, at least transiently, from opiates by resorting to alcohol consumption. The lowest prevalence rate is registered among subjects accepted for BMTP, considering that a selection bias exists among physicians, who generally welcome BMTPs as an option for addicts who show partial control of their heroin use at time of baseline evaluation.

With these premises, the meaning of baseline involvement with alcohol is not that of a higher grade of severity of the opiate-related pathology, as revealed by the lack of any influence on retention in treatment (12-14). In comparing the features of retained subjects in a partial vs. complete agonist programme (14), alcohol use is greater among methadone-maintained subjects who are more severely ill as a group. Later on, when the number of retained subjects shrinks, this difference is no longer recorded. A possible explanation is that, when the average grade of addiction severity is levelled through time by the progressive dropping out of more severely addicted subjects, heavy alcohol use tends to dwindle. Alternatively, the successful outcome of treatment programmes is linked to a reduction in alcohol consumption, but this effect is unlikely when methadone dosages stay below blocking values, as in the study sample. In France, buprenorphine has been the only available agonist treatment for years: in this situation, a lower grade of addiction severity (with a duration of addiction below ten years) and alcohol dependence were among the predictors of good response to treatment (21).

Alcohol use seems to be correlated with the severity and level of activity of opiate use disorder, without adding a heterogeneous element to the clinical picture, so that the likelihood of alcohol use control is linked with the likelihood of opiate use control by therapeutic regimens.

The rising suspicion of masked heroinism

All too often the evaluation of addiction treatment programmes is exclusively founded on the maintenance of abstinence from the original substance (street opiates) in the short
term, after enrolment. When other clinical aspects are accounted for, less satisfactory pictures may result: for instance, there is a rising trend towards alcohol use among self-detoxifying and detoxified heroin addicts who undergo naltrexone treatment, suggesting that alcohol serves as a means of compensation for the loss of heroin availability (10, 18, 19). Whatever heroin craving may emerge during the achievement of detoxification and enduring abstinence, addicts may succeed in providing clean urinalyses by shifting over to cross-acting substances. In the addict’s natural environment, before any therapeutic setting, alcohol consumption may compensate for the lack of heroin availability (due to poverty, somatic impairment, or temporary supply shortages), so becoming a common means of self-handling in a situation of opiate craving (17).

For heroin addicts, who have a strong motivation to “turn over a new leaf”, whatever is useful in staying detached from heroin may be resorted to on a regular basis. In the case of another addictive substance, such as alcohol or cocaine, an apparent state of remission actually takes shape as a switching form of addiction. An iatrogenic way of favouring the course towards an involvement with alcohol as a surrogate consists of omitting or interrupting an effective treatment for heroin addiction. A premature removal of agonist drugs, an easy availability of naltrexone programmes as the most suitable solution for low-severity addicts, medically supervised detoxification programmes, and drug-free regimens are all examples of interventions which directly favour, or fail to counter, a switching evolution of heroin addiction towards alcoholism. Conversely, if alcohol-abusing addicts are prompted with methadone treatment, that may forestall their alcohol consumption in the short term, so indicating a rapid direct action of opioid agonism on alcohol craving in this population (5).

A similar mechanism may limit the usefulness of agonist treatment in drinking addicts: when heroin use is the only parameter that influences therapeutic decisions, methadone dosages may stay lower, but overall improvement may be impaired by alcohol acting as a surrogate for heroin. In animal models (23), rats show they prefer an alcohol-methadone mixture to either alcohol or methadone alone, the latter being the least attractive to them. In particular, a higher alcohol/methadone proportion in the mixture corresponds to a higher level of appeal. This combination may reproduce a heroin-like effect, and appeal to addicts whose craving is not completely controlled.

Authors employing a wide variety of dosages were able to compare a group of subjects treated with high dosages (above 100 mg/die), with the others. While the results of heroin use showed only slight differences, higher methadone dosages were correlated with lower rates of alcohol and benzodiazepine use (15, 16). In our personal experience, we have ascertained the relationship between methadone dosage and depressant abuse in the same subject: an increase in methadone dosage was soon followed by a significant decrease in alcohol and benzodiazepine use (11). Programmes relying on low methadone dosages may therefore be spoiled by a high incidence of alcohol abuse, mirroring the incomplete control of opiate craving in the guise of alcohol-methadone coupling. As a result, it seems that methadone treatment, as long as no other feature is specified, actually favours the development of alcohol abuse (2).
Alcohol use in a high-threshold methadone maintenance programme

As for methadone programmes, the variability of alcohol use may depend on treatment features, chiefly dose and duration.

The PISA-SIA Group MMTP provides flexible dose long-term maintenance, in which effective dosages are reached, as a general rule deriving directly from physicians’ decisions, with no dose threshold, no duration barrier, and no room for rule manipulation by negotiation. Patients are given methadone at increasing dosages, on the basis of weekly clinical assessment and urinalyses, until clinical stabilization is reached (i.e. no more than one positive urinalysis for morphine in the previous two months and a DMS-IV GAF score above 60), so defining a positive outcome. Patients who fail to achieve stabilization by their first year of treatment are discharged from the programme. For those who are stabilized, any requests for dose decrease before two years of successful maintenance should be discouraged. With these premises, alcohol and cocaine use was measured by means of the Alcohol Craving Scale and the Cocaine Problem Severity Index, respectively (22).

Alcohol abuse has a 37.7% frequency (20 out of 53 consecutive responders at one year); in most cases it is linked with pre-existing involvement with alcohol (primary alcoholics or dually addicted individuals). The most likely impact of methadone treatment upon alcohol use is to reduce its relevance as a clinical problem, or even to end alcohol consumption altogether. Methadone dosage is not fixed at a higher level for alcohol abusers, which may indicate indirectly that, for these subjects, detachment from heroin use is partly achieved by methadone action, and partly by alcohol use. Extending Anglin’s hypothesis to all opiates (abused or therapeutic), opiate balance is self-handled by resorting to alcohol and/or opiates, in an inverse relationship. Other authors had also reported that a higher dosage is required for non-alcoholic addicts (20).

As long as subjects abuse cocaine alone, methadone dosage is significantly higher (130 vs. 65 mg/day on average, F 2.89, p = 0.04). When alcohol and cocaine are used together, no difference is registered, which may indicate an opiate-boosting function of alcohol, automatically limiting the need for methadone coverage. When subjects abuse alcohol as well as cocaine, the need for increased methadone dosages, as observed in cocaine-only users, is neutralized so suggesting that methadone and alcohol share a cocaine-counteracting property. In this sense, Anglin’s hypothesis could be extended to comprise substances, such as cocaine, which alter the opioid balance, and so induce the practice of resorting to pro-opioid factors in order to reverse their anti-opioid effect. In both cases, alcohol appears to function as an opioid surrogate, unfortunately not equivalent to methadone because of its long-term toxic effects and the intrinsic addictive liability it brings with it.

The Opiate Background of Alcoholics

To acquire the advantages of an alcohologist’s point of view, we reviewed 99 consecutive files of subjects visited at Rome “La Sapienza” University’s outpatient
treatment centre for alcohol-related pathology; they had all systematically undergone psychiatric evaluation based on DSM-IV criteria in conditions of sobriety. Fifteen subjects had a history of heroin addiction, but none of them had gone through any period of regular heroin use during the previous year (4 had used it at least once in the last year, 8 had not been using it for years). No differences emerged in terms of socio-anagaphical features or in chronology or quantity of alcohol use: age of first use, age of habitual involvement with alcohol consumption (i.e. daily regular use or recurrent intoxication occurring more than once a week), time interval from first use to habitual use, years of habitual use, amount of consumption at the beginning of habitual use and maximum amount ever consumed. Heroin addicts had greater psychiatric comorbidity, accounting for DSM-IV axis I psychiatric disorders, addictive disorders included, but excluding simple substance abuse (t -5.85; P < .001). When addictive disorders alone were considered, the divergence was sharper (t-7.79; P < .001:). No differences were noted as regards the prevalence of axis II personality disorders. Psychiatric comorbid disorders were found in 64%: affective disorders were first, in order of prevalence, anxiety disorders were far less well represented, and non-affective psychoses were rare. This order of prevalence was maintained when excluding substance-induced psychiatric disorders with a possibly transient course, so ruling out a sample of undoubtedly dual diagnosis alcoholics. Age of first contact with alcohol was, predictably, lower than that of first heroin use, whereas age of onset of alcohol dependence was usually higher. In most cases, the increase in alcohol consumption took place during periods of medically supervised withdrawal of agonist therapy, or after the accomplishment of drug-free residential programmes, or spontaneously during detachment from heroin use.

Psychiatric diagnosis was classified around the bipolar spectrum, dividing the sub-sample of dual diagnosis alcoholics into bipolars and non-bipolars; no significant differences emerged. Since bipolar II was the most frequent bipolar picture, the bipolar II/non-bipolar II dichotomy was also examined: a trend (p = 0.07) towards a greater prevalence of bipolar II subjects among alcoholics classified as “ex-heroin addicts” was observed.

Furthermore, when looking back on the therapeutic history of former heroin addicts who later applied for treatment as alcoholics, the most likely condition is the absence of any previous specific intervention. Two out of three had never entered an agonist-based treatment programme. For those who had entered one, maximum dosages were not always in the blocking range of 80-120 mg/day or above, and were not maintained in the long term, but tapered. Duration of methadone programmes was variable.

Conclusions

It seems that alcohol addiction can be viewed as a possible negative outcome of ongoing heroin addiction. Actual alcohol addiction is not the rule among heroin addicts. Nevertheless, alcohol abuse may set in or become worse in iatrogenic conditions, such as agonist treatment omission, ineffective dose administration, opiate-free regimens,
premature medication tapering or suspension. Adopting a different viewpoint, alcoholics with a history of heroin addiction proved in most cases to have undergone no agonist treatment or to have been treated with unjustified limitations on dosage or duration. This subgroup of addicts showed a higher level of engagement in substance abuse, as testified by a higher number of addictive diseases, but did not differ from their single diagnosis alcoholic peers as regards alcohol-related parameters. Alcohol-abusing heroin addicts seem to suffer from a metabolically acquired stain, which derives from preconditioning opiate abuse, and later prompts either opiate- or alcohol-seeking behaviour in an addictive way. The accomplishment of this metabolic destiny through a shift from heroin to alcohol use is subtle, as it may be mistaken for the remission of opiate addiction, whereas it appears to be just another pathological dynamic leading to opiate use extinction. Like the so-called masked depressive syndromes, alcohol abuse in former heroin addicts can be considered a masked form of heroinism, or a sign of enduring opiate dysfunction disguised as remission. The shift from heroin to alcohol also means the transition from a highly curable disease, as heroin addiction is, to one that is hard to cure, as alcoholism is. Alcohol abuse should be taken into account when judging which agonist dosage is adequate and whether treatment outcome is satisfactory on a prognostic basis. In other words, in cases of masked relapse / alcohol abuse with morphine-free urinalyses / agonist treatment should be resorted to, as with active heroin users, since alcohol abuse is likely to be a clinical sign of unhealed, persisting opioid damage.

References


Heroin Addiction and Related Clinical Problems


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Symptomatic treatment of opiate withdrawal syndrome by low-dose buprenorphine in an in-patient setting

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Summary

The present study aims to assess the effectiveness of buprenorphine treatment in countering predictable withdrawal from street opiates in 68 opiate-addicts who requested admission to an in-patient opiate detoxification facility. Buprenorphine was administered at flexible doses, on a patient-blind clinical basis. Withdrawal was assessed by scoring a range of symptoms at the start of treatment (T0) and three more times during treatment (T1-T3). The dropout rate was 14.7% and was not predicted by baseline clinical features. The average duration of treatment was 7.5 days. By then, buprenorphine had provided patients with quick-acting, stable protection against withdrawal symptoms and was well tolerated. Additional drugs were successfully resorted to when non-specific symptoms such as anxiety and insomnia were prominent. Buprenorphine proved effective in soothing withdrawal-related symptoms in a subgroup of mildly ill subjects. The short-term dropout in this population did not seem to be related to the severity of baseline withdrawal or to the absence of earlier improvement under buprenorphine.


Introduction

Over the years the gravity and pertinence of the issue of drug addiction have risen. Both the APA and the WHO have agreed that addiction is a chronic relapsing disease(1, 14), so bringing it to a higher level of attention in the public opinion. Given its chronic nature, addiction proceeds through phases of well-being alternatively with relapses of varying duration.

Most addicts, and, to their discredit, some healthcare workers too, generally mistake
a drug-free state for a sign of disease remission. Some addicts who have recently undergone detoxification apply for in-treatment at high-threshold centres, which would deny admission if any agonist-treatment was still ongoing. Other patients taper their methadone with a view to entering antagonist treatment with naltrexone, which requires them to be opiate-free before they can be enrolled.

No matter how strong their motivational drive, some patients fail to overcome withdrawal from their medication if they are left without pharmacological support. Moreover, some situations may require patients to taper quickly, so that special strategies to minimize discomfort are needed: in other words, patients may need an effective buffer against their complex withdrawal pictures.

Any healthcare operator dealing with addiction-related issues should know which symptoms may develop during opiate withdrawal. At the same time, it is quite uncommon to treat an opiate addict who is not also abusing other substances, as polyabuse is the rule in heroin addiction. Predictably, a polyabuser’s withdrawal syndrome is of a more complex type, as it is rooted in a combined tolerance to different substances, with a variable grade for each.

Our aim in the present study has been to assess the effectiveness of buprenorphine (BUP), at low doses, against opiate withdrawal alone, regardless of what symptoms may be due to abstinence from other substances. Buprenorphine is a partial \( \mu \)-agonist with a high receptorial affinity \((7, 10)\): in fact, it soon establishes a sound opioid blockade\((12)\), while no room is left for further agonist input, due to massive receptor binding (ceiling effect) \((13)\). Thus, the agonist effect tends to reach a plateau quite quickly, and cannot equal that provided by full agonists, either in terms of therapeutic potency or toxicity \((9)\). Unlike other anti-craving opiate drugs, buprenorphine has a \( k \)-antagonist effect \((7, 11)\), which may be responsible for tolerance-related issues but also for therapeutic peculiarities \((5)\). Buprenorphine has proved effective both in medically supervised withdrawal from heroin \((8)\), and in treatment programmes for opiate-addicted individuals \((6)\).

Methods

Sixty-eight opiate-addicted patients, were enrolled after they have been referred to a Government-financed Clinic for inpatient opiate detoxification by their GPs or the local Addiction Treatment Unit. Their mean age was 32 (range 21-49) and 9.6%, (63 patients) were male.

All these patients had been addicted to opiates for over six years, and were essentially injectors, inhalation being an atypical mode of administration for all of them. 13% had been using cocaine irregularly, mostly by a snorting mode. All were habitual smokers and had been taking benzodiazepine at much higher doses than prescribed. Alcohol use was unremarkable, and was never reported at such a level as to create an expectation of specific withdrawal.

The therapeutic schedule was not fixed, but left flexible, to allow adaptation to each patient’s needs. Treatment was started as soon as withdrawal symptoms emerged, by
administering 0.2 mg intravenous buprenorphine, followed by decreasing doses every 8-12 hrs.

Buprenorphine was administered intravenously into vessels leading to the upper caval system, in order to avoid the first-pass metabolism by the liver, which is responsible for an 80% conversion to the inactive 6-glycuronide metabolite (2-4).

Patients were blind to how much buprenorphine was being administered, since the amount of liquid vehicle did not vary with the buprenorphine dose, but was kept at around 100 ml of saline.

Withdrawal symptoms were assessed by a self-evaluation scoring system ranging from zero to five (0-5), zero corresponding to no symptom, and five to a subjective level of high intensity. Rated symptoms included sweating, tremor, muscular pain/spasms, running nose and nausea/vomiting. The self-evaluation scoring form was administered to patients at the start of the treatment schedule (T0-score), on the 2nd and 4th days of buprenorphine treatment (T1- and T2-score, respectively) and before discharge (T3-score) (Table 1).

All of our patients received benzodiazepine treatment to treat insomnia and anxiety: fast-acting, high potency benzodiazepines were chosen as hypnotics, whereas low potency, long-acting compounds were resorted to for an anxiolytic effect.

Results

Of the 68 patients admitted, 10 (14.7%) asked to be discharged on their own responsibility. Two of these had never started buprenorphine at all, while 8 others discontinued it, mostly on the 2nd or 3rd scoring day on the schedule.

Drop-outs did not differ from completers as regards age, sex or T0-score (Table 2– Figure 2).

Significant improvement was recorded between T0- and T1-score, both for drop-outs and treatment completers, while the two groups scored similarly at time 1 (Table 2). Score reductions were below significance into the two groups from T1 to T2, and from T2 to T3 (Figure. 1).

The baseline withdrawal-related conditions, as rated by T0-scores, do not seem to foretell either retention in treatment or treatment effectiveness.

On average, programme completers were hospitalized for 7.5 days (range 4-11) and were given an average cumulative dose of 235.5 ±14.7 mcg.

No major side-effects ascribable to the medication were observed. One patient experienced vomiting throughout the second day of treatment, and was given standard anti-emetics. Another patient reported a headache, which spontaneously disappeared on the 2nd day, and was thus of uncertain origin.

To sum up, the therapeutic schedule proved safe, and no major side-effects calling for treatment discontinuation were observed.
Table 1. Self-evaluation rating scale for opiate withdrawal symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>absent</td>
</tr>
<tr>
<td>Sweating</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
</tr>
<tr>
<td>Muscular pain/spasms</td>
<td>0</td>
</tr>
<tr>
<td>Running nose</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/Vomit</td>
<td>0</td>
</tr>
</tbody>
</table>

TOTAL

Discussion

As a premise, it must be noted that buprenorphine detoxification was intentionally practised for a subgroup of opiate addicts, who had absent/very low craving when applying for detoxification, and were highly motivated to undergo it because of their urgent need to discontinue agonist treatment, and/or to be enrolled in drug-free residential programmes.
Table 2. Comparison between responders and drop-outs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders (n = 58)</th>
<th>Drop-outs (n = 10)</th>
<th>Significance (p &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>93.1 %</td>
<td>90.0 %</td>
<td>ns</td>
</tr>
<tr>
<td>Age</td>
<td>31.98 ± 6.01</td>
<td>35.20 ± 7.80</td>
<td>ns</td>
</tr>
<tr>
<td>T0 Score</td>
<td>14.57 ± 1.72</td>
<td>15.90 ± 1.91</td>
<td>ns</td>
</tr>
<tr>
<td>T1 Score</td>
<td>6.26 ± 1.82 *</td>
<td>7.38 ± 2.54 *</td>
<td>ns</td>
</tr>
</tbody>
</table>

* T0-score vs T1-score: p < 0.001

Figure 2. Withdrawal scores

Compliance was high: 58 out of 68 enrolled patients (85%) completed treatment as scheduled, experiencing a satisfactory resolution of most withdrawal symptoms. Typical opiate withdrawal symptoms (vomiting, painfulness, sweating, runny nose and tears/weeping) markedly dwindled throughout the treatment period. A 30% reduction in global withdrawal discomfort was reported, which in itself was enough to classify the treatment as beneficial.

Anxiety and insomnia, which were challenged by anxiolytic and hypnotic drugs, must be considered separately: such symptoms are quite common during opiate withdrawal, but are usually a consequence of continued opiate use, too. In other words, they are a feature of opiate abuse regardless of ongoing withdrawal, and are best described as a...
harmful result of addiction itself, rather than as an outcome of acquired tolerance.

Despite the apparently strong motivation declared by all patients, 15% of them failed to continue after hospitalization, and dropped out. It remains unclear whether dropping out can be related to a flaw in motivation, or is a result of previously latent craving, evoked by the new perspective that the substance would no longer be available while on treatment. Moreover, personality traits may have played a role in favouring treatment discontinuation because of subjects failing to adapt to the environment of our Clinic. A subject with a borderline personality disorder, for instance, may feel coerced and victimized within that environment, even if admission has been voluntary. Future studies are now needed to evaluate the influence of psychiatric conditions, as assessed at baseline, on treatment retention. On the other hand, programme completers showed they were able to overcome the psychological discomfort raised by the withdrawal they had to face, and while in hospital they found greater support than that provided by pharmacological treatment alone. There is no doubt that environmental factors do weigh on the quality and intensity of opiate withdrawal as a subjective experience.

It is striking that 85% of patients completed their treatment schedule in spite of the persistence of some unpleasant symptoms, such as anxiety and insomnia, which made it necessary to maintain specific pharmacological treatment after discharge. However, without a placebo control, the contribution of psychological factors rather than pharmacological agents to success in overcoming opiate withdrawal cannot be clarified. It should be borne in mind that buprenorphine was administered at low dosages, and that no significant differences between T0- and T1-scores emerged in comparing completers and dropouts, so no clear treatment effect can be identified. As many as 85% of treatment starters completed the programme, so various different factors could have contributed to this result. The combination of a minor pharmacological effect, provided by buprenorphine, and a reassuring environment is likely to ensure that patients achieve a satisfactory outcome, but no clue is available so far to allow the relative weight of either component to be determined.

Conclusions

Parenteral low-dose buprenorphine administered along a short-term decreasing-dose schedule proved effective in the treatment of opiate withdrawal in an in-patient setting, for as many as 85% of the patients admitted. Treatment was considered viable for patients who showed a low level of craving or none at all, and a strong need to discontinue agonist treatment in view of a drug-free residential treatment. Safety was high, since side-effects were never such as to require treatment interruption. Hospitalization may have been a key factor contributing to a positive outcome. Although a minority of patients experienced notable anxiety and/or insomnia, these symptoms were successfully treated by adding on benzodiazepines. With these features, an 85% retention rate was achieved throughout the study. The schedule adopted showed it was suitable for the treatment of opiate withdrawal in a subgroup of patients selected by
the above criteria at study entrance.

References


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Also by Fax
Open letter to physicians and other health care providers facing pain management during opioid agonist therapy with methadone

J. Thomas Payte

Both maintenance treatment providers and consumers are aware of the all-too-frequent and unnecessary failure on the part of treating physicians and dentists to provide adequate treatment for pain in patients being treated with methadone. This may be a result of a lack of information, simple misunderstanding, or unfortunately, at times associated with prejudice toward patients with opioid dependence being treated with methadone.

This brief correspondence is to provide simple guidelines that are evidence-based and supported by years of clinical experience.

Patients being maintained with methadone require special considerations for acute pain management in surgical or trauma situations. Methadone Maintenance Treatment (MMT) patients are often denied any analgesia and serious under-treatment of pain is very common. MMT patients develop full tolerance to the analgesic effects of the medication (methadone). During MMT a cross-tolerance develops to all opioid agonist drugs accounting for the “blockade” effect. Early research demonstrated that stable MMT patients could not distinguish 20 mg IV morphine from IV saline. The usual maintenance dose does not provide any analgesia, and adequate analgesia will require higher doses of opioid agonists given with greater frequency than in a non-tolerant patient.

Methadone has a half-life of 24-36 hours but analgesic effects are from 4-6 hours, similar to morphine in both potency and duration (Goodman & Gilman). Morphine, dilaudid, codeine, etc. are appropriate for the treatment of acute pain in the MMT patient.

Mixed agonist/antagonists (Talwin, Stadol, Nubain) and partial agonists (buprenorphine) must not be used as they will precipitate opioid withdrawal. Meperidine and propoxyphene should be avoided due to risk of seizures at the higher doses required to produce analgesia in opioid tolerant patients.
Summary:
1. Continue maintenance treatment without interruption. This provides a background in which other treatment may be effective.
2. Provide adequate individualized doses of opioid agonists which must be titrated to the desired analgesic effect. The proper dose is enough! Due to cross-tolerance the doses will likely be significantly higher than those in opioid-naïve patients.
3. Doses are usually provided more frequently than in opioid-naïve patients. Pain that is not relieved 1-2 hours will not improve by waiting for a 3-4 hour interval. Inter-dose intervals should be adjusted to prevent the onset of pain, not in reaction to a recurrence of pain.
4. Please call the patient’s program physician above for further information.
   Please treat our patients with the compassion, dignity, and respect that they deserve as you would expect us to treat a patient of yours that might need our services at some time.

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