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UK INJECTABLE OPIOID TREATMENT TRIAL (RIOTT)

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"This blind pursuit of cheapness that we have with treatment is mistaken; if a treatment does not deliver benefit, it is the worst of all options, and ineffective treatment is inefficient and cannot be cost effective no matter how cheaply it is provided. It is amazing this is so obvious once it is pointed out to you."

John Strang

Prof. John Strang has served on committees writing guidelines about injectable prescribing, has worked with a range of pharmaceutical companies (including work on alternative heroin formulations that were better or cheaper than heroin), has been in charge of leading a provider organisation, and has worked with charities and other policy review organisations. Here, he discussed the clinical outcomes from the Randomised Injectable Opiate Treatment Trial (RIOTT). He also provided a history of prescription heroin in the UK.

Sarah Byford presented cost analyses and discussed the economic results of the RIOTT Trial.

RIOTT: HISTORY OF THE TRIAL

The Randomised Injectable Opiate Treatment Trial (RIOTT) was an attempt to find treatment for people addicted to heroin for whom other treatments had failed. The essence of the study was to determine whether injectable opiates might be able to 'turn around' the lives of people for whom other, more 'orthodox' treatments had been unable to help, even if this option turned out to be more costly.

The trial was approached with quite a high level of ambivalence; that is, there was no loyalty to any particular modality or outcome – even though all involved had a necessary sense of advocacy about the field (without which no one would conduct a

controversial, difficult study) and complete loyalty to the addictions field and the scientific process – and not everyone may be a complete convert.

The UK has a rich history in addiction going back about a century; back to before the Ralston Report, which recognised that addiction has a substantial medical component. This raised the question of whether a medical or law enforcement response was required, and the UK took the path of a medical response. Even though the term ‘maintenance’ was not used, the UK therefore established that in appropriate circumstances, the continued supply of injectable morphine or diamorphine was a legitimate medical practice, strongly diverging from the US view. Injectable heroin was therefore never prohibited – it just fell out of favour because of the strength of other options, specifically the growing evidence for and credibility of oral methadone and buprenorphine over the past 40 years. These two options have been widely adopted, while others withered away, raising an interesting research question: Is there something about injectable heroin or injectable methadone that we might be missing out on?

When Ambros Uchtenhagen came over to the UK 15 or 20 years ago to observe our heroin prescribing practices, about 1% of people in treatment were receiving heroin, and even though for quite a long time ~10% of patients had received injectable methadone, this, too, had dwindled to 1%. What he observed was therefore fairly unimpressive – a ‘blunt and rusty penknife’ that we were about to throw away. He then returned to Switzerland and converted our practice into a gleaming Swiss Army knife – essentially the same tool, but refined and re-imagined. The particular innovation, in this instance, was the supervised heroin clinic. In the UK, patients were coming in and were given supplies to take home, which inevitably leaked into the black market. The Swiss, with due Swiss efficiency, said “this is a problem we can solve” – and they did.

The RIOTT Trial, thinking that the Swiss had done a pretty impressive job, therefore decided to bring the Swiss Army knife back into the UK. That essentially is what the RIOTT Trial is.

Part of the birth right of the RIOTT Trial was that the feasibility of this approach was already being explored in the UK. The 2002 UK Drug Strategy had suggested that heroin should be available by prescription to all those with a clinical need. However, this was incredibly vague, as it left open the meaning of ‘clinical need.’ The RIOTT Trial therefore chose epidemiology-based needs-assessment terms to define it as ‘the ability to benefit, particularly where one had not benefited from other treatments.’

The strategy defining how the trial would be run also stated that it would take place in safe, medically supervised areas with clean needles, and that it would use strict and verifiable measures to ensure there was no risk of seepage into the wider community. This was the essential blueprint for how the clinics should be set up, and the focus was decided to be on the repeatedly failing patient.

Of course, cost is an important factor to consider, and will be discussed in more detail by Sarah Byford. From a doctor’s perspective, the priority is to work out whether an intervention will save a patient’s life or turn their life around. It is therefore a concern that cost appears to have become a dominant issue while the benefit to the patient has become secondary.

For optimised oral methadone maintenance treatment (i.e., oral methadone combined with something more than just the drug), the costs are about £5,000 per patient per annum. In comparison, supervised heroin clinics cost something like £15,000 per patient per annum, while supervised injectable methadone is about £10,000 per patient per annum (although these figures are not completely accurate, as will be explained by Sarah Byford). People typically think that that these costs are terribly high, but it is important to remember that court-mandated ordinary methadone treatment is about £10,000 per patient per annum, and prison, according to Hansard, is £44,000 per inmate per annum. Also, it has been said that the blind pursuit of cheapness is shallow, and that no matter how cheaply a treatment is provided, if it does not deliver benefit it cannot be cost-effective and is the worst of all options.

RIOTT: IMPLEMENTATION AND RESULTS

Going back to the nature of the supervised injection clinics, the key characteristic in their operation is that they are open and under supervision seven days a week. Although many were quite excited when the decision was made to go ahead with this project, the excitement was not equally shared by the staff who were told they had to work 365 days per year. However, it is a bit like a casualty department, an A & E department; it must surely always be open whenever there might be need for it.

Another feature is that there are no take-home injecting doses. Of course, people have lives to lead, so the clinics have become much more accommodating about a conversion to an oral equivalent, but there are no take-home injections.

The treatment facilities are fairly unremarkable; the rooms are drawn up in a very medical way, deliberately medicalised to remove the surroundings from the previous behaviour. The patients come in and self-administer the heroin, after which they are checked to make sure they are safe, and then they go home.

The trial involved 127 such patients, randomised into 3 groups receiving either supervised heroin, supervised injectable methadone, or enhanced oral methadone. The key measure, or primary outcome, was street heroin use, with the reasoning that if the treatment was not seriously denting their use of street heroin, it could not possibly account for any other benefits. For this, the research team had to develop a urine test to differentiate between pharmaceutical heroin and street heroin, which was fairly successful. Secondary measures included patient well-being.

Treatment retention was rejected as an outcome measure, as it was considered potentially cheating, in that a treatment could result in good retention without actually having any real health gain. In the RIOTT trial, it was the actual gain that was of interest, along with the ability to capture a signal of any benefit over noise. It was also suggested that the primary outcome be absolute abstinence from street heroin, but this may fail to capture important changes; the team therefore focused on major reductions in use, while also reporting whether patients became completely abstinent. This was an improvement over some of the earlier trials, along with the urine testing alongside self-report.

The results showed unequivocally that the supervised heroin group had the strongest improvements. The supervised injectable methadone group showed the next best

improvements, and both were better than the oral methadone group. Interestingly, the oral group also improved, presumably due to some degree to the 'Hawthorn Effect' (people benefitting because of increased attention) and the availability of the facilities. Also of note is how incredibly quickly these improvements were seen.

A trial is a bit like a race: you set off your three groups, and you want to see who does best at the six month mark and how many are doing badly. The RIOTT results showed that everyone was doing catastrophically badly at the start (i.e., urine absolutely full of street heroin) – which was actually a relief as a researcher, because if anybody is doing well, they were chosen wrongly.

In both the oral methadone and the injectable methadone group, about a quarter to a third had made quite a substantial improvement by the 6-month mark (i.e., random urine tests mostly or fully clean for street heroin). This is quite interesting, as the oral group had been chronically failing on oral before, and just by taking them into a trial, a quarter of them suddenly improved. This shows that what is currently done can be improved.

In the supervised heroin group, on the other hand, three-quarters substantially quit their street heroin use at six months, as gathered from random urine tests during the later months. Of these, 20% completely quit street heroin use, while 40% gave 12 of 13 'clean' urine samples (i.e., not a complete set but a pretty impressive result) and more than 50% gave 11 of 13 'clean' samples. This is especially amazing considering that these are people who had been using heroin for about 17 years, who had been in and out of methadone treatment, in and out of rehabs, in and out of prisons, battle scarred veterans of the treatment and the criminal justice system. In contrast, almost nobody from the other two groups completely quit street heroin use, and only 10% gave 11 of 13 'clean' samples – a hugely different outcome.

Another way to assess outcomes is by a 'numbers-needed-to-treat' analysis. This method estimates the size of an effect by calculating how many patients would have to go through the trial in order to get one who 'survives' or shows a response (who otherwise would not have shown it); the smaller the number, the more powerful the treatment. The RIOTT results showed that only two patients needed to go through the treatment to get one who showed a benefit that wasn't there before – an extraordinarily powerful effect.

Results also showed that in the oral methadone group, the proportion of the group giving clean urine slowly drifted up over the course of 6 months. But in the heroin group, extraordinary results were visible within six to eight weeks. Analysts are now exploring how robust that finding is, because it suggests that one should be putting people into this treatment. If it indeed shows robust effects within 2-3 months, then one is onto something very productive; but if not, then one can abort an expensive treatment and fail more cheaply.

The trial also included numerous safety measures. There were several serious adverse events related to the treatment, but as mentioned by Prof Uchtenhagen, compared with the condition being treated it is comparatively safe. No deaths related to the treatment have been reported to date, despite some life-threatening situations; including serious overdoses, which, if not for the very good staff, could have become deaths. This also points to why the programme cannot be run with lower costs, minimal staff and

volunteers, etc. – it would soon run into disasters. Careful pulse oxymetry measures can monitor patients' oxygen levels (since opiates decrease respiratory drive, which underlies overdose deaths), and one needs people to monitor these carefully, as changes are more unpredictable than one may think.

There is now an accumulating body of evidence from studies around the world: the original Swiss study, along with studies from the Netherlands, Germany, Canada, and the UK. It is a strong body of evidence which is consistent in its findings.

The 2008 Government Drug Strategy document now mentions implementing prescription of injectable heroin and methadone, subject to findings from the RIOTT Trial. However, it should be viewed as an intensive care sort of treatment (i.e., only for clients who do not respond to other forms of treatment – the most severe 5-10%); one cannot do it in a casual flippant way, and it must be done competently. The treatment has its own inherent risks, but that is not a reason not to do it.

In terms of next steps, members of the Department of Health and the National Treatment Agency for Substance Misuse (NTA), which includes several of the team working with the RIOTT Trial, are reviewing the Trial and devising an Action Plan Document 2011/2012. The NTA will work with the Department of Health to pilot the cautious roll-out of this type of supervised treatment and monitor the small number of people who may benefit from it.

RIOTT: THE COSTS

There is a lot of evidence to suggest that injectable treatments for heroin addiction are much more expensive than alternative methods, and yet there is a lot more evidence indicating that they are clinically much more effective.

Injectable treatments are more expensive due partly to the cost of the drugs themselves, but also due to the additional dispensing and supervision resources which are key to this kind of treatment. The question is whether they are an unaffordable luxury, but it is not possible to give an answer just by looking at the cost of the treatments. The value for money is also influenced by the outcomes that are generated, as well as any cost savings that may occur in the health system or other systems.

The aim of the economic evaluation of the RIOTT Trial was to explore cost-effectiveness in relation to two outcomes: first, the primary outcome of the trial (responders negative for street heroin), and second, 'quality-adjusted life years' (the measure preferred by the National Institute for Health and Clinical Excellence (NICE), the body responsible for guidelines in the UK). NICE had strongly encouraged the team to look at the Quality-Adjusted Life Years (QALY) measurement. They were, however, fairly sceptical about whether quality of life would change in this population, and it was a tough test.

Regarding health and social services (the perspective preferred by NICE), service utilisation patterns showed that most of the participants lived independently, but many still used hostels and shelters relatively frequently; this number was much higher in the oral methadone group than the other groups. Similarly, syringe exchange use was much higher in the oral methadone group.

In the criminal justice sector, a very small number of patients were spending nights in prison or police custody, and it was actually amongst the crimes committed in the 26 weeks where the real difference was found. On average, participants in the optimised oral methadone group committed 21 crimes over 26 weeks, which was substantially higher than the injectable groups. Commonly committed offences (~20%) were theft from shops and handling stolen goods. Other relatively frequent crimes were begging, theft from a vehicle, and soliciting prostitution, but those were actually carried out by a very small number of the group as a whole. What was found was a very small number of very prolific offenders, and a large proportion of the population who were not committing crimes at all. Looking at differences between the groups, the proportion of participants committing crime was much lower in the injectable heroin group than the other two groups, and the number of crimes was approximately 1/3 the number committed by the oral group.

As mentioned by Prof. Strang, the cost of the intervention in the heroin group had to be considered, as it was much higher than the others. This group was the most expensive to treat, with injectable methadone in the middle, and oral methadone the least expensive. Adding other health and social services to the cost, plus criminal justice sector contacts (e.g., with police, solicitors, etc), the differences between groups remained much the same. However, when adding the cost of crimes committed, the difference switched from injectable heroin being the most expensive to oral methadone being by far the most expensive of the groups.

These were the economic outcomes of the trial. Although the injectable heroin group had a slightly higher QALY, these differences were smaller and it was quite a tough test for the injectable groups.

Taking a quick look at what this means for cost-effectiveness, comparing injectable heroin with oral methadone shows that heroin is more effective and less expensive, if one includes the costs of crimes; i.e., it is the more cost-effective option. For the NICE in the UK, an intervention has to cost £30,000 per QALY or less to be considered cost-effective. The analysis shows there is a ~68% probability of the injectable heroin being more cost-effective. The results are the same for injectable methadone; it is more cost-effective than oral methadone, irrespective of what society is willing to pay for a QALY. This was the secondary analysis, and it gives an idea of what the trade-off is between heroin and injectable methadone. Injectable heroin was more effective but it was also more costly. On the other hand, supervised injectable methadone had a higher probability of being more cost-effective.

Differences in heroin prices were also examined, as cost-effectiveness varies with the cost of the heroin itself. Discussions with current suppliers suggested that supply might be feasible at a slightly lower cost than was paid by the RIOTT Trial, and if there was an increase in demand and thus changes to production, future supply would probably be even cheaper. Therefore, as the price goes down, the probability of injectable heroin being more cost-effective creeps up slightly.

Analyses also very briefly examined the impact if one was to ignore criminal justice. NICE in prefers to look at the perspective of health and social services, and this effectively reverses the conclusion. Oral methadone is more cost-effective than both injectable options because it has far lower intervention costs, but only small differences in QALYs. However, from a clinics perspective, in the National Health Services at the

moment there is huge pressure on resources. Therefore, providing injectable treatments greatly increases cost of these clinics, while they are not seeing the savings; these all go to the criminal justice service. From a broad perspective, it is therefore obvious that injectable treatments are more cost-effective than oral methadone, but the cost-effectiveness is being driven by the criminal justice sector. There may need to be some discussions about compensation for the clinics who are paying a lot more to support these treatments but are not receiving any of the savings.

Finally, if we are looking at injectable heroin versus injectable methadone, the clinical evidence that Prof. Strang presented before suggests that injectable heroin is more effective than injectable methadone. However, the economic evidence is less clear, which gives the opportunity for clinics to consider other factors than just cost-effectiveness, such as, for example, patient preference. It is necessary to clinically assess the need and also the affordability of it, and to determine whether the clinic can provide it.