# Ranking the harm of non-medically used prescription opioids in the UK

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**Running head:** ranking prescription opioids

**Key words:** opioids, MCDA, risk assessment, ranking, prescription drugs, harm,street heroin

**Word count:**5159, including references

**SUMMARY**

A panel of nine experts applied multi-criteria decision analysis (MCDA) to determine the relative overall harm to users and harms to others of street heroin (injected and smoked) and eleven non-medically used prescription opioids.The experts assessed harm scores for each of the 13 opioids on each of 20 harm criteria, weighted the criteria and explored the resulting weighted harm scores for each opioid.

Both forms of heroin scored very high: overall harm score of 99 for injected heroin and 72 for smoked heroin on a scale of 0-100. The main feature that distinguishes both forms of street heroin use is that their harm to others is more than five times that of the other eleven opioids. The overall harm score of fentanyl (including injection of fentanyl extracted from patches) and diamorphine (medically prescribed form of heroin) was 54 and 51, respectively, whereas that of orally used opioids ranged from 32 (pethidine) to 11 (codeine-containing pharmaceuticals).Injected street heroin, fentanyl and diamorphine emerged as most harmful to users, with the latter two very low in harm to others.Pethidine, methadone, morphine and oxycodone are also low in harm to others, while moderate in harm to users.

We conclude that the overall harms of non-medically used prescription opioids are less than half that of injected street heroin.These data may give a basis for precautionary regulatory measures that should be considered if the rising trend in non-medical use of prescription opioids were to become evident in the UK.

**INTRODUCTION**

Prescription opioids are non-medically used for a variety of reasons, mostly because they give benefits ranging from pain relief to euphoria. For non-medical use a variety of definitions are used in the studies described in literature. Here, after discussion, non-medical use was defined as "taking too much and/or too long" for whatever reason, where too much and too long are defined as discordant with the usual medical use of the drug. This definition encompasses use not prescribed, or beyond that prescribed, as well as use with no medical sanction or intention.The type of opioid use that was evaluated by the experts in the current study was 'non-medical or illicit use' of prescription opioids.

Over the pasttwo decadesin the U.S.andto a lesser extentin Canada,the use ofopioid analgesics,especiallyoxycodone (OxyContin), increased 10 to14-fold (Manchikanti et al., 2012).

Thisincrease followedaliberalization of thelawinprescribingopioid analgesicsbytheFederation of State Medical Boards, which encouraged doctorstobemore proactivein identifying andtreating chronicpain(FSMB, 1998). As a consequence, in the U.S., the number of opioid prescriptions delivered by pharmacies between 1991 and 2011 increased from 76 to 219 million (Volkow, 2014). Furthermore, between 1999 and 2008, the four-fold increase in the prescribing of opioid analgesics was paralleled by a four-fold increase in both the number of opioid dependent people (from 2.2% to 9.8%) and the number of fatal opioid related overdoses (CDC, 2011). In the U.S. in 2012, 75% of all fatal incidents with pharmaceutical products wererelated to opioids (Jones et al., 2013) and 420,000 visits to the emergency departments were opioid related(SAMHSA, 2013). Therefore, the increased misuse of opioid analgesics and the clear increase in opioid-related morbidity and mortality in the U.S.was labelled by the CDC as one of the top five health threats for 2014 (CDC, 2013).

In the past two decades, the use of opioid analgesics also significantly increased in Europe (DCAMC, 2012, Ruscitto et al., 2014, Zin et al., 2014, Schubert et al., 2013, Bandieri et al., 2009, Garcia del et al., 2008, Poulsen et al., 2013, Fredheim et al., 2010, Hawton et al., 2012, NHS, 2011),but it is unlikely that in the UK and elsewhere in Europe the non-medical use of prescription opioids will become as prevalent as in the U.S.(Fischer et al., 2014, Weisberg et al., 2014). In the U.S. opioids are widely available as they are often given by family and friends or can be obtained by "doctor shopping" or purchased from semi-legal and illegal pain clinics. For a review about the misuse of prescription opioids, see van Amsterdam and van den Brink (2015).

In comparison, access to more potent opioid medications for pain relief in the UK seems to be limited due to the stricter legislation and regulation and the efficient control of both the prescription and the delivery of opioid analgesics using electronic patient records.However, it has been shown that 30% of UK patients with opiate substitution prescriptionssold,gave away or swapped their medication (Dale-Perera et al., 2012), explaining the relatively high misuse of diverted opioid substitution medication amongst drug using populations in England and Scotland, mainly by out-of-treatment opioid users(Stöver, 2012), compared to other drug using populations in European counties (Dale-Perera et al., 2012). The increased use of opioid analgesics in Europe was not accompanied by an increase in the misuse of these drugs or an increased number of fatal incidents. While in the U.S. the use of opioids between 1999 and 2008 (in morphine equivalents per person per year) increased from 350 to 700 and the number of drug deaths doubled from 6 to

12 per 100,000, the use of opioids in Britain increased from 100 to 300, but the number of drug deaths remained stable at 6 per 100,000 (Weisberg et al., 2014). These data suggest that in the U.S. the widespread use of opioid analgesics has increased the prevalence of opioid abuse, whereas in the UK misuse of prescribed opioids is predominantly misuse of formulations prescribed as heroin substitutes, which tend to be less risky than misuse of heroin and other street opiates.

If the non-medical use of prescription opioids were to increase in Europe, this would be from a relatively high baseline, so future precautionary regulatory responses may be needed. Therefore, the relative overall harm of eleven non-medically used opioid analgesicswas evaluated, using street heroin as a reference. This is important as the problems in the U.S. and Canada occur mainly with three specific prescription opioids: hydromorphone, oxycodone and fentanyl (Fischer et al., 2014).

## METHOD

Nine experts with expertise in either drug addiction or pain treatment(8 from the UK, 1 from the Netherlands and all listed as authors of this paper) were invitedto take part in this assessment by DrugScience.org.uk (formerly known as the Independent Scientific Committee on Drugs or ISCD). The experts' specialisms included addiction,substance abuse, addiction psychiatry, health psychology, pharmacology, psychopharmacology, toxicology and veterinary science.

The experts attended a two-day facilitated workshop(Phillips, 2007)to assess the actual and potential harmsrelated to the 'non-medical or illicit use' of eleven prescription opioids for whatever reason they were used. In addition, injected and smoked street heroin were evaluated for comparison. Illicit or non-medical use of opioids can create harms to users and harms to others, a distinction that had been used before in the assessment of the overall harm of alcohol, tobacco and a number of illicit drugs (van Amsterdam et al., 2010, van Amsterdam et al., 2015, Nutt et al., 2010).

All experts were guided by the facilitator (LP) through the methodology and the principles of multi-criteria decision analysis (MCDA)as they constructed a model of overall harm (Nutt et al., 2010, Nutt et al., 2014). The 16 criteria used in these studies were taken from the Nutt et al. 2010 study [25] as a starting point. However, the criteria 'Specific impairment in mental functioning', 'Injury', 'Environmental damage' and 'International damage' werevery slightly modified to

reflect the narrower scope of the current study. In addition, four new criteria were used coveringthe concerns of the expert group related specifically to opioids:‘drug interactions’: extent to which this drug could interact with other drugs to increase harm; ‘tolerance’: the risk of overdose death following loss of tolerance after abstinence or greatly reduced use; ‘availability’: extent and ease of obtaining a supply; ‘altered prescribing’: inhibition of clinically indicated prescribing due to concerns regarding the potential for dependence and diversion.The 20 criteria were clustered under five subheadings covering the following domains: (1) physical,(2) psychological and (3) social harm to users, and (4) physical and (5) social harm to others (cf. Fig. 1). Each criterion was carefully explained to the experts by the facilitator which enabled them to evaluate allopioids in a consistent and meaningful way.

The following 13 opioids were selected for ranking:injected street heroin, smoked heroin, transdermal fentanyl (including injected fentanyl extracted from patches),pharmaceutical grade injectable diamorphine usually prescribed for treatment of heroin dependence pethidine, methadone, morphine, oxycodone, buprenorphine, tramadol, suboxone (buprenorphine + naloxone), codeine + dihydrocodeine, and compound codeine products.The routes of administration considered included oral, snorting, chewing (patches) or i.v. injection.

**Scoring principles**

The experts scored the criteria directly one by one following the harm tree shown in Figure 1 from top to bottom. The facilitator ensured that all viewpoints were aired, judgements were backed with data if available, and bias was minimised by selecting the most harmful drug for each effect and making assessments (e.g., by applying the ‘think, speak, debate’ sequence of the nominal group technique(Gustafson et al., 1973), which prevents each participant from anchoring their judgement on that of the first person to speak).Per criterion each expert had first to consider his/her score together with an argument before sharing the score with the group. After sharing the scores and their subsequent justifications the final integral score of the expert group was obtained via consensus. This procedure applied both to harm scores as well as to the rating of weighting factors.In making their judgements, participants frequently referred to published data, which were discussed for their representativeness and quality, and debated in light of experience with users.This enabled the group to construct consensus harm scores that represented the participants’ collective judgement in light of the evidence and available experience. Occasional marked

disagreements were noted and tested in sensitivity analyses.This scoring process is specifically designed to minimise bias(Phillips, 2007).

**Scoring procedure**

First, the most harmful opioid on a given criterion was identified and agreed by the group.That opioid (and any others deemed equally most harmful) was given a harm value of 100, with zero representing no harm; these two points established a ratio scale.Second, each of the remaining opioids was assigned a harm value as a percentage representing the ratio of judged harm compared to the most harmful opioid on the criterion (e.g., an opioid judged to be half as harmful as the most harmful one was given a harm value of 50).

**Weighting the effect scales**

Weight factors were given to each harm criterion to weight the relative importance of each harm criterion to the overall harm of the 13 opioids.This was accomplished by assessing a separate swing-weight (scale 0-100) for each of the criteria, the swing from no harm at all to the most harmful drug on a given criterion.After the weights have been normalised so they sum to 100 over all 20 criteria (which preserves their original ratio to one another), the weights are known as 'cumulative weights' and represent the difference in judged harm between no harm and the most harmful opioid on each effect.The harm score for an opioid on a given effect scale is multiplied by the cumulative weight for the scale, and those products are summed over the 20 criteria, giving an overall weighted preference score for each opioid.

**Sensitivity analysis**

Finally, the group explored the results and conducted sensitivity analyses to determine the extent to which uncertainty in the data and differences of opinion could change the overall ordering of opioids.

**RESULTS**

**Ranking the opioids**

Table 1 shows the cumulative weights associated with each criterion.Note that 16 of the 20 criteria each contribute 3% to 9% of the total weight with the highest values for Drug specific

mortality, Tolerance, Crime and Economic costs. Drug relatedimpairment of functioning, availability, altered prescribing and environmental damage together contribute only 3.6%.

Considering the recent widespread misuse of prescription opioids in Canada and the U.S., it should be highlighted here that the availability of opioids was scored 100 for codeine compounds (OTC; freely available in pharmacies), 90 for injected and smoked heroin and 50 for methadone. The remaining opioids were scored below 30. As stated above, data from England and Scotland indicate that illicit methadone and buprenorphine diverted from prescriptions are readily available in the illegal drug supply system. Moreover, the weight factor for availability was only 0.9.

A graphical presentation of the individual contributions of weighted scores of the 13 opioids for the 20 effects (260 scores) is complex and not legible in a grey-scale display so only the overall score of harm to others and harm to users is presented in Figure 2. Note that the sum of the cumulative weights for the 11 harm scales for users is 60%, and is 40% for the 9 harm scales for others.

The ranking of the opioids in Figure 2 clearly shows that injected street heroin and smoked street heroin are the most harmful of these 13 opioids. Injected heroin was scored 100, most harmful, on 11 of the 20 harm criteria, while although smoked heroin scored 100 on only four harm criteria, it scored 70 or above on 10 additional criteria. The main feature that distinguishes both heroin opioids from all the other opioids is that street heroin isover five times more harmful to others. The other 11 opioids are all much lower in their harm to others (value below 6.6 on the scale from 0 to 100), while varying in their harms to users.

Injected heroin, fentanyl + and diamorphine emerged as most harmful to users, mainly because these three opioids are dosed intravenously which has a high risk of harm from overdosing during non-medically supervised use. Similarly, smoked heroin is considered less harmful for the user than injected heroin, because with smoking the dose can be titrated and tends to be limited by the user’s degree of intoxication. Pethidine, methadone, morphine and oxycodone were ranked as lower in harm to others, while moderate in their harm to users.The remaining five opioids are less potent opioid agonists (buprenorphine, tramadol, suboxone, codeine comb. and codeine)that are all lower in harm to users and in harm to others.The small 1-point difference between compound codeine products and codeine resulted from markedly different characteristics: compound codeine was considered as more harmful on drug specific damage to the users (due to the potential for paracetamol overdose), whereas codeine was more harmful mainly because of

itshigher tolerance.

Plotting the harm to users against the harm to others (Figure 3) clearly indicates that smoked and injected heroin were scored as the most harmful opioids for others (appearing in the right upper quadrant) while fentanyl + and diamorphine are equally harmful for users, but much less harmful to others (right lower quadrant).

**Sensitivity analyses**

Because street heroin is the most harmful opioid on harm to the user and on harm to others, it maintains its position as the overall most harmful drug whatever the weight on users or others.All other opioids became more harmful overall as the weight on the harm to users was increased,whereas only smoked heroin became less harmful with more weight on the harm to users. It appeared that unrealistically large changes for a few of the harm criteria were required to make a serious difference, implying that the model is very robust to differences in the judgements about the weights on the individual harm criteria. However, a few opioids showed substantial changes in their ranking when the weights on certain criteria were increased. Compound codeine was particularly susceptible: increasing the weight on 'drug specific damage' or on 'availability' caused compound codeine to move up the rank order: the more weight, the higher the rank. Diamorphinewas especially sensitive to the weight on 'altered prescribing'; increasing the weight on that harm to a little more than 30% moveddiamorphine to the most harmful position after injected street heroin.

Once the final ranking was obtained and presented, the participants found the overall results to be a reasonable representation of overall harm; they realised that testing their few early differences in judgements would not reveal any substantial change in the overall ordering of the 13 opioids.

**DISCUSSION**

The main finding of this study is that the overall harm of a variety of non-medically used prescription opioids is less than half the overall harm of injected street heroin. For the most part this difference emerges from the high harm that is elicited by the use of (injected and smoked) street heroin. For pethidine, diamorphine and fentanyl+ the harm for the user was at least half as high as injected heroin's user harm, which shows a considerable risk if used non-medically.At the other end of the spectrum, codeine preparations and suboxone (a buprenorphine-naloxone

combination) had the lowest overall harm scores.

The relative overall harm of a variety of licit and illicit recreational drugs for the user and for others was previously assessed in two independent studies using a similar methodology (Nutt et al., 2010, van Amsterdam et al., 2015). The set of substances in these studies held three drugs in common with the present study i.e. heroin, methadone and buprenorphine. Pearson correlation coefficients of 0.90 to 0.98 for input scores on each of the 16 criteria these two studies and thepresent study held in commonwere calculated, providing substantial support for the reliability and validity of scores generated by the groups, at least for the three opioids considered in each analysis. Apparently, the group deliberation and discourse provided scores for these three substances that were consistent and replicable.

Process validity derives from the soundness of the social process, i.e. decision conferencing.Research on decision conferences(Schilling et al., 2007, Chun, 1992, McCartt and Rohrbaugh, 1995, McCartt and Rohrbaugh, 1989) and group workshops(Franco and Montibeller, 2015, Phillips, 2011, Schilling et al., 2007) has identified four features that contribute to validity: competence of the experts(Shanteau, 1992), diversity of perspectives in the group(Shanteau, 2001), impartial facilitation by a facilitator who guides the process but does not contribute to content(Phillips, 2007), and development on-the-spot of a model that is based on sound theory(Regan-Cirincione, 1994), in this case, decision theory(Dodgson et al., 2000, Keeney and Raiffa, 1976).All of these factors were applied, as far as was practically possible, in designing and conducting the decision conference that was used for this study.

It should be noted here that while the magnitude of the harm for the different criteria can be informed by data, the magnitude of weighting factors is not based on data and remains exclusively a matter of judgement. On the other hand, however, the comparison of unweightedoverall harm scores can be misleading and one should remain careful not to over-interpret the findings. Finally, we would like to mention that the applied MCDA approach has been criticised (Caulkins et al., 2011). Caulkins et al. (2011) proposed an alternative approach that also included the benefits of the different substances. However, Caulkins' approach probably makes it even more difficult to establish a one-number estimate for the (net) harm of substances and the validity of his approach is unknown. Moreover, it should be noted that in contrast to the risk-benefit evaluation of pharmaceutical compounds, the score in drug evaluation is only meant as a measure of harm because in recreational drug use there is no illness and no potential clinical

benefit.

The present assessment corroborated the low availability of prescription opioids in the UK (except for codeine), considering the low scores on the criterion 'availability'. Secondly, both in the U.S. and the UK opioid painkillers and heroin share a common market (Weisberg et al., 2014; Inciardi et al., 2009), but the price of heroin in the U.S. is about 7-8 times higher compared with the UK, which may have prevented or at least retarded the development of an illegal market and misuse of opioid analgesics (Weisberg et al., 2014). For these reasons it would be of interest to repeat this MCDA harm assessment in the USA.

This analysis shows there are very significant differences in the relative harms of the various non-medically used opioids. Street heroin whether injected or smoked was ranked as the most harmful opioid in the UK today followed by non-medically used prescription opioids such as diamorphine and fentanyl patches. Unexpectedly, oxycodone turned out to be only moderately harmful. This contrasts with the extensive abuse of this specific prescription opioid in the U.S. and Canada. The explanation could be that oxycodone was "aggressively marketed and highly promoted" in North America (Van Zee, 2009) leading to a more than 20-fold increase in sales in four years, more than all other prescription opioids and much more marketing than is allowed for any opioid in the UK. This illustrates that drug harms are not independent of prevalence of use. The current findings have implications for the provision of pain treatment and could provide a basis for precautionary regulatory measures should these become necessary due to a future increase in non-medical use of prescription opioids. However, such measures should be proportionate and not restrict or obstruct the treatment of chronic pain and heroin dependence.

The group finally agreed that it would be of value to include real or perceived benefits of drugs in a future MCDA exercise as it was important to recognise drivers for illicit drug taking including pleasure, pain relief or escape from negative cognitive states. However, it was agreed this would double the length of the exercise and should be the focus of a future decision making exerciseprovided that funding could be found.

**Participants**

Experts: James Bell, Owen Bowden-Jones, Annette Dale-Perera, Richard Hammersley, Graeme Henderson, Jan Melichar, John Ramsey, Polly Taylor and Jan van Amsterdam. Facilitators: David Nutt and Lawrence Phillips.

**Funding**

Funding was provided by an unrestricted educational grant to DrugScience from RB pharmaceuticals.

**Declaration of interest:**David Nutt has served on advisory Boards for BMS, Lilly, Shire, Lundbeck, Servier, Pfizer, Reckitt Benkiser, and D&A pharma. He has received speaking honoraria from these companies and also from Janssen, BMS, GSK, and Schering-Plough. He is a member of the Lundbeck International Neuroscience Foundation.

Polly Taylor acts as independent consultant in veterinary pharmacology and pharmacokinetics to Abbott Laboratories. Dr Polly Taylor has provided consultancy services for the manufacturer of buprenorphine in the UK (Alstoe Animal Health).

Wim van den Brink reports personal fees from Mundipharma, grants from Alkermes, during the conduct of the study; personal fees from Lundbeck, Indivior, D&A Pharma, Novartis, Bioproject, Pfizer, outside the submitted work. The other authors declare no conflict of interest.

**Legends to figures**

**Figure 1.** The 20 harm criteria for prescription opioids. See Nutt et al. 2010 for details.

**Figure 2.** The opioids ranked by their overall weighted harm scores, with the stacked bar graphs showing the contribution to the overall score of harm to others and harm to users with a cumulative weight of 40.0 and 60.0, respectively. Injected heroin: street heroin taken intravenously; Smoked heroin: smoked street heroin;Fentanyl +: non-medical use of patches, including injection of fentanyl extracted from patches; Codeine Comb.: compound codeine products.

**Figure 3.**Harms to Others versus Harms to User relative to injected heroin. 1: Injected heroin; 2: Smoked heroin; 3: Fentanyl+; 4: Diamorphine and 5: Pethidine.

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**Figure**

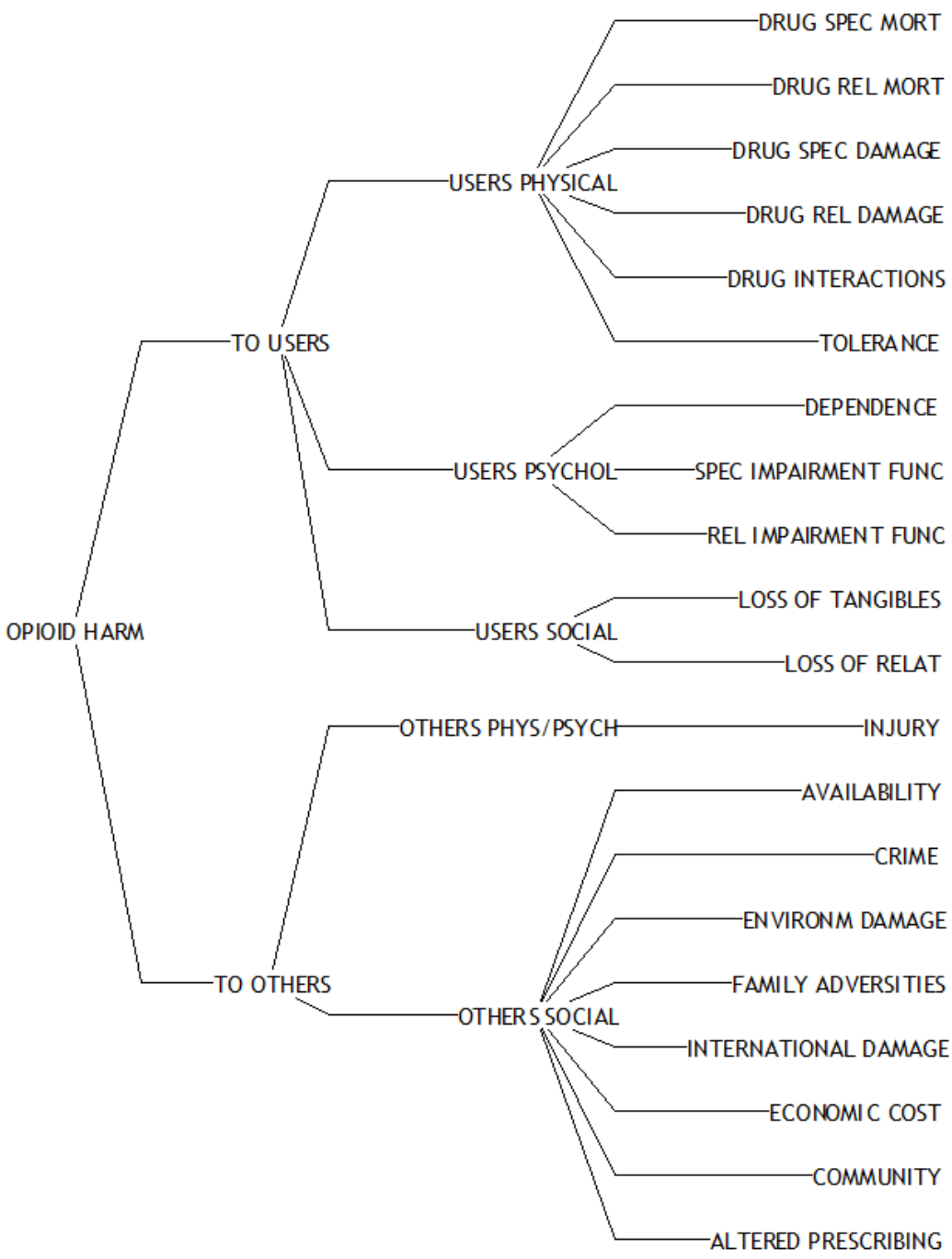


**Figure 1** The 20 harm criteria for prescription opioids. See Nutt et al. 2010 for details.

**Figure**

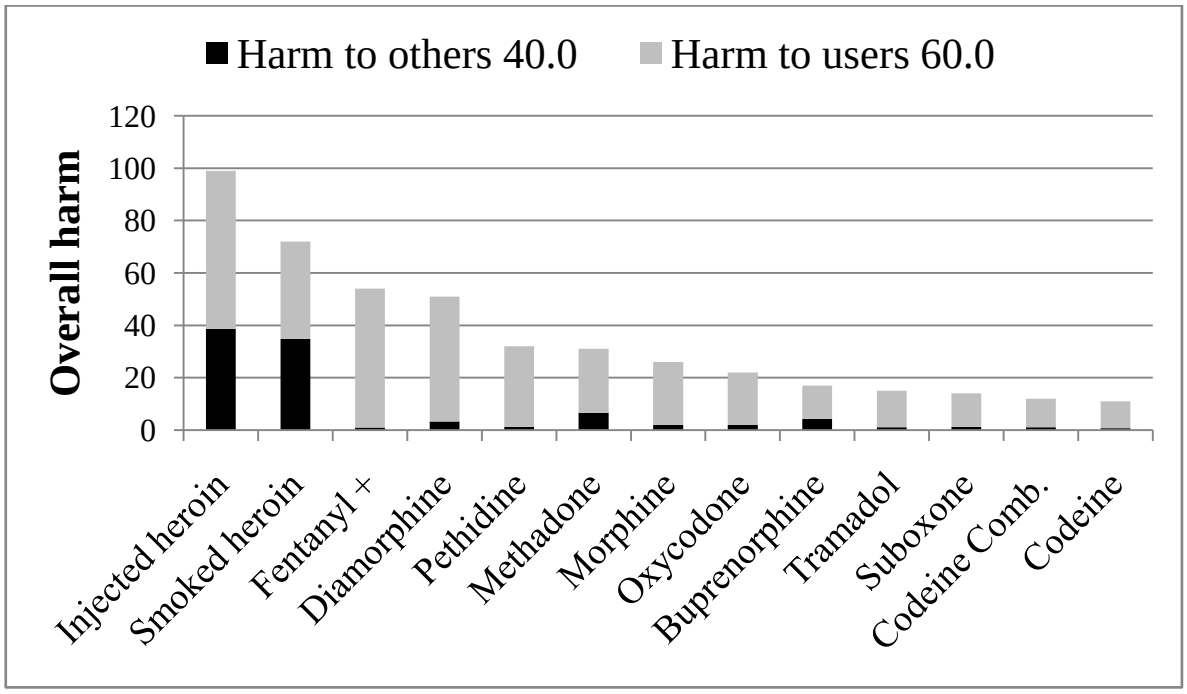


Figure 2: The opioids ranked by their overall weighted harm scores, with the stacked bar graphs showing the contribution to the overall score of harm to others and harm to users with a cumulative weight of 40.0 and 60.0, respectively. Injected heroin: street heroin taken intravenously; Smoked heroin: smoked street heroin;Fentanyl +: non-medical use of patches, including injection of fentanyl extracted from patches; Codeine Comb.: compound codeine products.

**Figure**

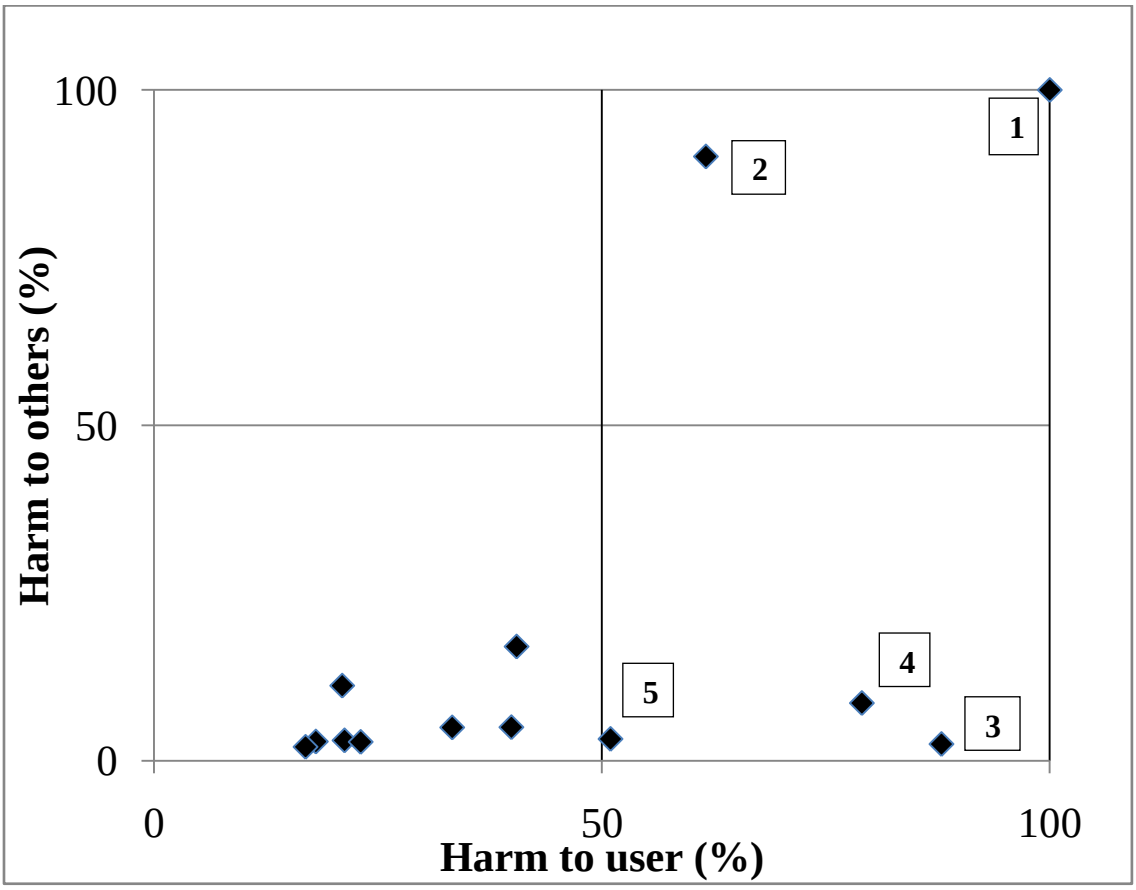


Fig 3.Harms to Others versus Harms to User relative to injected heroin. 1: Injected heroin; 2: Smoked heroin; 3: Fentanyl+; 4: Diamorphine and 5: Pethidine.

## Tables

Table 1. Cumulative weight of the 20 criteria

| Name | Cumulative weight |
|---|---|
| **Drug specific mortality** | 8.8 |
| **Drug related mortality** | 7.5 |
| **Drug specific damage** | 5.7 |
| **Drug related damage** | 5.7 |
| **Drug interactions** | 5.7 |
| **Tolerance** | 8.8 |
| **Dependence** | 5.7 |
| **Drug specific impairment of mental functioning** | 4.2 |
| **Drug related impairment of mental functioning** | 1.4 |
| **Loss of tangibles** | 3.0 |
| **Loss of relationships** | 3.5 |
| **Injury** | 5.3 |
| **Availability** | 0.9 |
| **Crime** | 8.8 |
| **Environmental damage** | 0.4 |
| **Family adversities** | 7.9 |
| **International damage** | 3.5 |
| **Economic cost** | 8.8 |
| **Community** | 3.5 |
| **Altered prescribing** | 0.9 |