Use of multicriteria decision analysis for assessing the benefit and risk of over-the-counter analgesics

MOORE, Andrew, CROSSLEY, Anne, NG, Bernard, PHILLIPS, Lawrence, SANCAK, Özgür and RAINSFORD, Kim

Published version

MOORE, Andrew, CROSSLEY, Anne, NG, Bernard, PHILLIPS, Lawrence, SANCAK, Özgür and RAINSFORD, Kim (2017). Use of multicriteria decision analysis for assessing the benefit and risk of over-the-counter analgesics. Journal of Pharmacy and Pharmacology, 69 (10), 1364-1373.

Use of multicriteria decision analysis for assessing the benefit and risk of over-the-counter analgesics

Andrew Moore (1), Anne Crossley (2), Bernard Ng (2), Lawrence Phillips (3), Özgür Sancak (2), K.D Rainsford * (4)

1. *Pain Research, Nuffield Division of Anaesthetics, University of Oxford, Oxford, UK*
2. *Reckitt Benckiser Consumer Health, Slough, UK*
3. *Department of Management, London School of Economics and Political Science, London, UK*
4. *Biomedical Research Centre, Sheffield Hallam University, Sheffield, UK*

Abstract: Objectives : To test the ability of a multi-criteria decision analysis (MCDA) model to incorporate disparate data sources of varying quality along with clinical judgement in a benefit-risk assessment of six well-known pain-relief drugs. **Methods**: Six OTC analgesics were evaluated against three favourable effects and eight unfavourable effects by seven experts who specialise in the relief of pain, two in a two-day facilitated workshop whose input data and judgements were later peer-reviewed by five additional experts. **Key findings**: Ibuprofen salts & solubilised emerged with the best benefit-risk profile, followed by naproxen, ibuprofen acid, diclofenac, paracetamol, and aspirin. **Conclusions**: MCDA enabled participants to evaluate the OTC analgesics against a range of favourable and unfavourable effects in a group setting that enabled all issues to be openly aired and debated. The model was easily communicated and understood by the peer reviewers, so the model should be comprehensible to physicians, pharmacists, and other health professionals

Key words: OTC analgesics, MCDA, group judgements, decision conferencing, pain relief

1. Introduction:

Providing safe and effective over-the-counter (OTC) medications for minor (non-serious) ailments is an increasingly important part of many healthcare systems. Simple analgesics are available without prescription in most countries worldwide for the symptomatic treatment of acute, self-limiting painful conditions [1, 2]. Recent EU data shows that 47% of consumers have used an OTC analgesic once per week in the last month [3]. No study has directly compared all these analgesic active ingredients and conventional meta-analyses cannot do full justice to the complex array of data on all their risks and benefits. Most of the data relating to the efficacy, and most particularly, the safety of these medicines derives from clinical studies conducted in the prescription setting in chronic conditions and with higher doses used for more prolonged periods of time than in the OTC setting. MCDA was employed as a novel approach to combining the available data across criteria to provide an explicit and succinct benefit-risk balance.

In 2012 the European Medicines Agency (EMA, formerly the EMEA) updated the EU regulatory framework [4] with what are now considered amongst the most significant changes for the regulation of medicines in the EU since the establishment of the EMA in 1995. The goal of this new legislation is to promote and improve the safety of medicines and facilitates the introduction and continual improvement of

Corresponding author: K.D. Rainsford, Ph.D., Emeritus Professor, of Biomedical Sciences: *. Email: k.d.rainsford@shu.ac.uk

benefit-risk evaluations.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) at their meeting on 25th June 2015 agreed in their work plan to focus on methodologies for the benefit-risk decision-making process[5], highlighting the importance of robust, transparent and reproducible decision making when interpreting clinical data by groups of experts.

Demonstrating how the positive and negative features of a medicine balance is difficult and largely subjective [6]. Computer-based models exist which analyse multiple criteria to assist with benefit-risk evaluations. These models enable enhanced quality and consistency of decision making based on the interpretation of best evidence by experts. One such model provides the opportunity to review existing data and produce a multi-criteria decision analysis (MCDA). MCDA has already been used to assess benefit and risks of prescription drugs [7-10] and the harms of psychoactive drugs [11, 12]. This study extends that research to over-the-counter (OTC) analgesics.

Analgesics vary considerably in terms of their relative efficacy and safety. Factors involved include the pharmacological and toxicological properties of individual drugs, their patterns of use, and patient-related factors [13, 14]. Making assessments of benefit and risk for the current range of simple OTC analgesics has not been easy. Reasons include:

- decision-making methods have not been standardised,
- results have not been easily reproducible by independent third parties,
- there are a wide range of factors, confounders and biases that have to be considered, and
- there is a degree of uncertainty in the interpretation of benefit and risk.

Individual clinical studies and meta-analyses have investigated safety and tolerability outcomes or one or more measures of efficacy. However, as far as the authors are aware, there is no single study comparing the overall benefit-risk ratios of these medicines. The aim of this MCDA was to assess and compare the relative benefit-risk balance of the most common single-active, oral systemic analgesics available over the counter (OTC) in the EU.

2. Methods:

2.1 Study Design:

A group of scientific experts specialising in pain relief, consisting of independent experts from academia (authors KR and AM), as well as scientists from industry (authors AC, BN and OS), undertook a benefit-risk assessment of six well-known OTC pain-relief drugs: aspirin (analgesic dose), diclofenac potassium, ibuprofen acid, ibuprofen salts and solubilised formulations (ibuprofen S&S), paracetamol, and naproxen sodium. Experts were chosen based on their well-established clinical and scientific expertise and professional standing in pain relief to include a diversity of experience in analysing and interpreting data in the areas of efficacy and safety.

The MCDA process was conducted over a two-day facilitated workshop held in Hull on the 17th – 18th September 2014. A similar model developed in 2010 to analyse the harms of a range of drugs in the UK [11] was used as a starting point, and adapted to assess the overall

benefits and risks of each drug. A computer program, Hiview3, was used for data entry, analysis and visualisation [15]. A summary of the methodology is set out in Appendix 1. Although RB participants were present during this process, they did not participate in the construction of the Hiview model. Briefly, eight steps were followed to analyse and interpret the data [16]:

1. establishing context with respect to the need for a robust benefit-risk assessment tool;
2. agreeing on the products to be evaluated and producing definitions of these;
3. agreeing on the criteria on which the products should be compared;
4. scoring the products on each criterion;
5. weighting the criteria;
6. calculating weighted scores to give an overall index of the benefit-risk balance of each product;
7. examining results and resolving any inconsistencies, and
8. exploring the sensitivity of the indices to different assessments of scores and weights.

The OTC analgesics to be evaluated were chosen based on the following characteristics. They should:

- be indicated for patients over the age of 18 years for short-duration use in acute pain,
- be available for purchase over the counter in the UK, and, to some extent, in Europe and rest of the world,
- contain a single active ingredient,
- be supported by robust publicly available data.

Since the impact of solubility of ibuprofen on pharmacokinetics and analgesic efficacy is well established [2, 14, 17-19], ibuprofen S&S have been included separately from standard ibuprofen acid. Diclofenac potassium is a salt formulation designed for immediate release and is available OTC in some parts of the world and effective in acute pain [20], and was included, while diclofenac sodium available on prescription was not. The following OTC medicines were agreed to be considered by the group: aspirin (analgesic dose), diclofenac potassium, ibuprofen acid, ibuprofen S&S, paracetamol, and naproxen sodium.

2.2 Criteria on which the products were compared

The experts considered three benefits (favourable effects) and eight risks (unfavourable effects) for the chosen drugs, taking into account the intended use of these drugs for the symptomatic treatment of acute mild to moderate pain with lower doses than prescription doses for a short period of time. The eleven effects are shown in Figure 1, with the unfavourable effects grouped under adverse reactions and serious adverse reactions, plus overdose toxicity.

[Insert Figure 1 about here]

Favourable effects

For OTC use, the desired characteristics of a good analgesic agent are providing good pain relief to a high proportion of subjects taking the medicine, speedy onset of action, and long

duration of action. Therefore, the three favourable effects of clinical relevance in the model were:

- pain relief, proportion of patients suffering moderate to severe pain who report at least 50% pain intensity reduction over 4-6 hours. This is the outcome generally recognised in systematic reviews and meta-analyses of single dose oral drugs in acute pain, and is the subject of a Cochrane overview review of OTC analgesics [14].
- speed of onset:- time to perceptible pain relief in minutes.
- duration of action:- time to remedication for 50% of the patients measured in hours.

Unfavourable effects

The unfavourable effects were categorised into 3 groups as adverse reactions, serious adverse reactions and overdose toxicity.

Unfavourable Effects - Adverse Reactions

Since analgesics are used at low doses and for short treatment periods in the OTC setting, only adverse reactions that may lead to treatment discontinuation of mild to moderate severity were considered. Thus, the incidence rates and severity of the following were included in the model:

- skin reactions such as rashes, pruritus,
- gastrointestinal (GI) complaints such as dyspepsia, nausea, vomiting and diarrhoea, flatulence, constipation, and abdominal pain,
- hepatic reactions such as mild, reversible elevation of liver enzymes and mild reversible elevation in bilirubin.

Unfavourable Effects - Serious Adverse Reactions:

Adverse reactions that are life-threatening, lead to death, require hospitalisation or medical treatment, or result in persistent or significant disability are considered serious. While these are rare (≥1/10,000 and <1/1000) to very rare (< 1/10,000) with OTC analgesics, the consequences might be devastating. Therefore, incidence rate and severity of the following four effects have been taken into account in the model:

- GI effects such as GI ulceration, bleeding, melaena, haematemesis and perforation,
- cardiovascular (CV) effects such as heart failure, hypertension, myocardial infarction and stroke
- renal effects such as acute renal failure
- severe allergic and hypersensitivity reactions such as anaphylaxis, Stevens - Johnson syndrome (SJS), Lyell's syndrome (toxic epidermal necrolysis), asthma and bronchospasm.

Unfavourable Effects - Overdose toxicity:

While overdose is rare with these drugs, considering the wide availability and potentially life threatening consequences of toxicity in overdose; the extent, severity and nature of toxicity in

accidental or intentional overdose was included as an additional unfavourable effect in the model.

The key references from which the evidence was sourced are summarised in Appendix 2. The final effects tree included 3 favourable and 8 unfavourable effects, shown in Figure 1.

2.3 Scoring the drugs on the criteria

The group agreed a hierarchy of evidence quality to assess data for the model in the following order: Firstly; systematic reviews, meta-analyses and, randomised controlled trials. Secondly, where the evidence was not definitive or unclear, cohort studies, case-control studies and cross sectional surveys were assessed, along with data from the UK summary of product characteristics (SPC).

In situations where the evidence and SPC were not clear or not comparable, clinical judgment by the independent academic experts took preference.

Inputs for pain relief, duration of action, speed of onset and skin reactions are expressed in natural, measured units (table 1). The group directly assessed preference values of 0 to 100 for the other effects after discussing available data and, where necessary, pooling multiple sources of data subjectively.

Hiview3 converted these measured units linearly into preference values, with the least and most preferred drug for each effect assigned preference values of 0 and 100, respectively. As reliable data for the remaining seven unfavourable effect were unavailable, the group directly assessed preference values on 0 to 100 scales, which represented participants' consensus about relative strengths of preference. In constructing these judgements, participants discussed available data, and considered their experience and knowledge of how the drug acts on the body, pooling these multiple sources of information subjectively.

[Insert Table 1 about here].

2.4 Weighting of the criteria

Some criteria are more important expressions of benefit or risk than others, (e.g. minor GI effects versus anaphylaxis), so weighting of the criteria was required. The purpose of weighting is to ensure that the units of relative benefits and risks on different scales are equivalent, thus enabling weighted scores to be compared and combined across the criteria.

To assess weights that are meaningful in MCDA, it was necessary to consider the differences in effects between highest and lowest scoring products on that criterion, and to establish how much that difference in effect matters in a given context, or in other words 'how big is the difference and how important is it'

Weights were elicited in the decision conference by asking the experts to compare the swing in preference from the least preferred drug on a given effect to the most preferred, as compared to the swing on another effect. For example, the swing on pain relief from aspirin to ibuprofen S&S was judged to be greater than the swing on duration of action from paracetamol to naproxen.

The weighted scores for each analgesic were summed to give an overall index of the benefit-risk ratio. Hiyiew calculated the weighted scores and provided displays of the results. Sensitivity analyses were also performed using Hiview3 by varying the weightings of the effect criteria to see how the overall results might change.

2.5 Peer review process:

To further validate the output and ensure that a robust interpretation of the data was performed, the authors completed a peer review exercise on 3 March 2015 to examine the quality and clinical interpretation of the data entered into the MCDA model. This involved inviting 5 European experts (see acknowledgements) to review the data, scores, and weights that had been input into the MCDA model. The peer reviewers also debated issues and again reviewed the model outputs during a face-to-face half-day meeting. This also allowed additional sensitivity analyses to be performed by comparing the scores of the drugs before and after the peer-review process.

3. Results:

The final weighted preference scores, before and after peer review, are presented graphically in Figure 2. The peer-review process confirmed ibuprofen S&S as the most preferred OTC analgesic for its benefit-risk ratio, and aspirin at least preferred. The Pearson correlation coefficient between these scores is 0.91.

[Insert Figure 2 about here]

During the peer-review process, a small change in the score on the *adverse reaction* for GI effects, from 100 to 90, and major changes to scores on *serious adverse reactions* for GI effects and overdose toxicity were introduced. While these changes did not affect the ranking of ibuprofen S&S, naproxen sodium or ibuprofen acid, they increased the overall weighted preference score of diclofenac from 31 to 54, moving it from fifth place in the ranking to fourth place, close to the score for ibuprofen acid of 57. The overall score for paracetamol remained at 39, followed by aspirin, whose score decreased from 28 to 13. The original experts accepted these changes and the results.

The six drugs differed from one another in various ways, as can be seen by the varying sizes of the coloured sections of the bar chart in Figure 3. The cumulative weights for the effects (normalised to sum to 100, but preserving their original ratios) are shown. Ibuprofen S&S remained the most preferred of these six, as it scored 100 on 3 of the most heavily weighted effects (overdose toxicity, pain relief and speed of onset). In addition, ibuprofen S&S as can be seen from Figure 3 was overall more beneficial and better tolerated than the others, so it remained the most preferred for any relative weights between favourable and unfavourable effects.

[Insert Figure 3 about here]

Comparing the weighted preference scores of pairs of drugs, one with another, showed the relative advantages of each drug in the pair. For example, ibuprofen S&S compared with paracetamol (Table 2) showed better pain relief, longer duration of action and faster speed of onset, with less overdose toxicity. Other quantitative comparisons showed that ibuprofen

S&S compared with naproxen was better for overdose toxicity, pain relief, speed of onset and serious GI effects, while naproxen sodium was better for duration of action. Comparisons of all six drugs, taken two-at-a-time, i.e.15 paired-comparisons, were consulted in drafting the text summaries of each drug shown in table 3. It is this kind of summary that might be most useful to clinicians.

[Insert Table 2 about here]

[Insert Table 3 about here]

Changing weights over their possible range from 0 to 100 revealed the extent to which the results are sensitive to the imprecisions in judging weights on the effects criteria. Multiple sensitivity analyses examining variations in the weight of each factor, particularly serious adverse reactions, serious CV effects, anaphylaxis and overdose toxicity, showed that only substantial changes in weights would lead to an analgesic other than ibuprofen S&S as the most preferred drug (Figure 4). Sensitivity analyses showed that the order of preference scores for the drugs did not change over very large ranges for the individual weights. Results from the MCDA model were robust to changes in weights of the criteria and the nodes.

[Insert Figure 4 about here]

4. Discussion:

Information about analgesics for OTC doses and duration of use is limited. While clinical trials exist either with placebo or against an active comparator, these are typically of single doses over hours [14]. Studies have not specifically been conducted to assess the benefit-risk balance of OTC analgesics. OTC analgesics are considered to be safe and effective, almost by definition: if a positive benefit-risk profile had not been rigorously demonstrated then these products would not be approved for OTC use, typically at lower doses in the short term. Most of the existing evidence underpinning analgesic use derives from knowledge and clinical experience with prescription analgesics used at higher doses and for prolonged periods. In making benefit-risk assessments we have only lower-dose short-term efficacy data, and higher-dose long-term adverse event and risk data. The challenge is to find a way to use these disparate data sources to make a judgement. MCDA offers a way forward for OTC analgesics, and we have tested the method here for 6 OTC analgesics.

The MCDA process provides a structured framework within which we can examine the many different aspects of making a specific judgement based on those aspects of efficacy and safety that are considered important. There are three stages – deciding what is important, rating the evidence for each aspect for each drug, and then ensuring that the output of the MCDA model make sense.

But we did not rely solely on our own judgements. It was important to reality-and-fact-check the evidence used and judgements made by submitting our work to a separate panel of independent academics with an even broader experience of analgesic efficacy and safety. This process made small amendments to our judgements, resulting in no major change to the results of the MCDA analysis. The use of an independent panel improves quality control and

ensures that no important factors or knowledge are being omitted from the decision analysis process. Alternatively, we might originally have chosen for our first meeting a larger panel of experts; some research suggests that groups above about six in size do not add much accuracy [21].

An overall summary of the assessments that were obtained following the final peer-review process is shown in Table 3. These assessments prove a practical means of selecting the safer or more effective drugs amongst those that were examined in this study.

The results of our MCDA analysis showed that, at typical OTC doses, fast-acting formulations of NSAIDs were more favourably assessed, namely ibuprofen S&S, naproxen sodium, ibuprofen acid and diclofenac potassium over paracetamol and aspirin. Evidence published since the MCDA panel met in 2014 reinforces the case for NSAIDs over paracetamol [22-28]. It is noteworthy that in the UK the National Institute for Health and Care Excellence (NICE) "identified reduced effectiveness of paracetamol in the management of OA compared with what was previously thought" [29], though the ultimate outcome of the discussions following this led to paracetamol being reinstated as first-line treatment [30]. Various steps are being taken in the USA to cut risks from paracetamol [31].

The cardiovascular risk associated with the use of NSAIDs has been the source of considerable research. The very large CNT (Coxib and traditional **NSAID** Trialists') analysis of randomised trials concluded that using NSAIDs at high doses in (mainly) arthritis trials was associated with a small increased risk of all-cause mortality, by about 20% compared with placebo [32], though the number of events with placebo was small. Subsequent observational studies have come to differing views, with some reporting increased event rates with NSAIDs and others, especially long-term longitudinal studies, reduced events [33]. The problem is that people with chronic pain have increased rates of cardiovascular disease and a 20% increased all-cause mortality in any event [34]. A major factor usually ignored is the negative effect of mobility in chronic pain conditions; lack of mobility tends to increase mortality in chronic pain [35]. These confounding factors are not often considered.

A recent study suggested an increased risk of heart failure with NSAIDs in a dose-dependent manner and called for further research into the safety of OTC NSAIDs [36]. The accompanying editorial suggested that paracetamol or weak opiates might be good choices without giving any consideration to their benefit-risk balance, and that more restricted policies on the availability of NSAIDs by regulatory authorities is warranted [37]. Our MCDA has demonstrated that fast-acting formulations of NSAIDs used over short periods at low doses have better overall benefit-risk profiles compared to paracetamol, and highlights the importance of a comprehensive and balanced assessment of benefits and risks, rather than focusing primarily on risks and mitigation of those risks.

5. Conclusions

The MCDA model described by Keeney and Raiffa [38] , is a useful tool for comparison of multiple favourable and unfavourable effects, data types and clinical judgments in a single model. It provides a framework that enables objective and reproducible benefit-risk assessment. Output is comprehensible to physicians, pharmacists, and other health professionals.

This analysis indicated that amongst the most common six simple OTC analgesics, ibuprofen S&S is associated with the most favourable benefit-risk profile, mainly owing to its low overdose toxicity, good pain relief, and fast onset of action. It is closely followed by naproxen sodium which performed somewhat less well on pain relief, speed of onset and overdose toxicity, but better on duration of action. Fast-acting OTC Non-Steroidal Anti-inflammatory drugs (NSAIDs) are associated with more favourable benefit- risk profiles compared with paracetamol.

Figures and Tables:

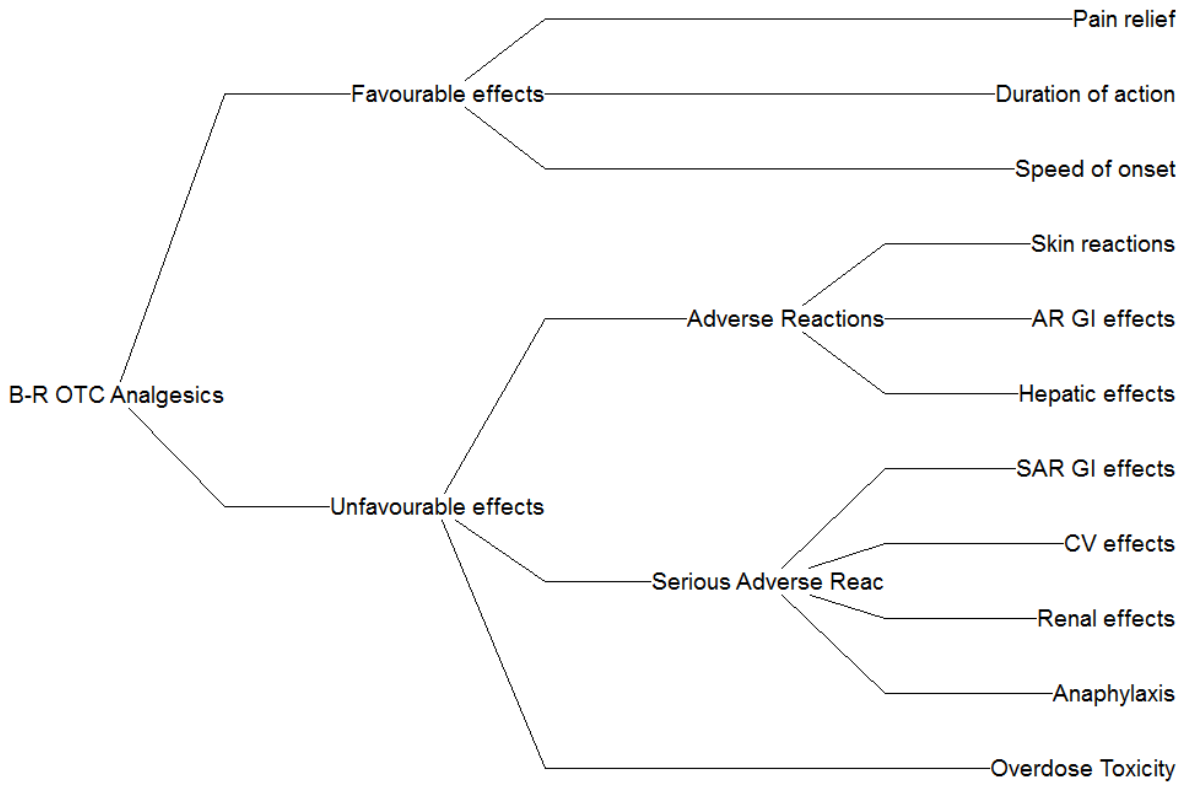

Figure 1: The final Effects Tree

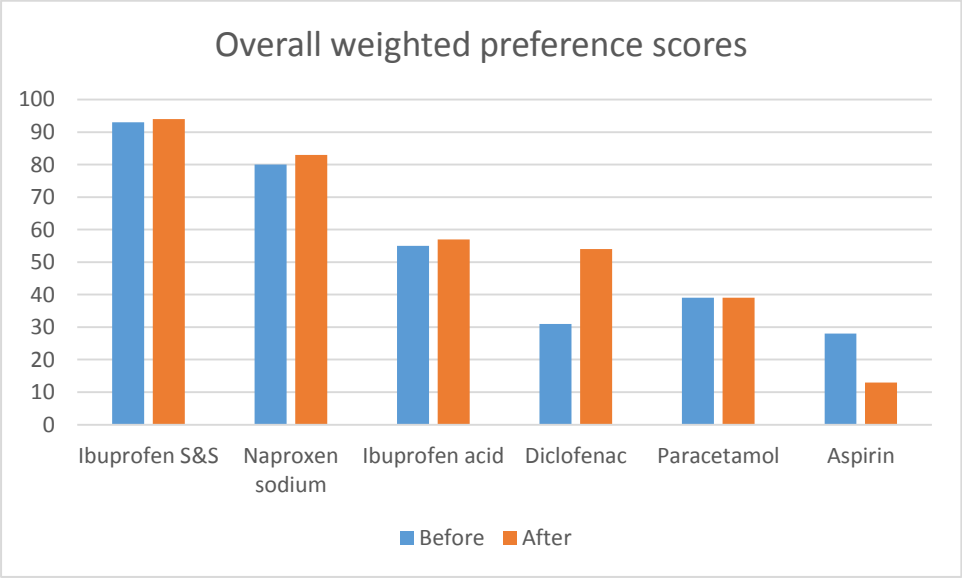

Figure 2 - Overall weighted preference scores before and after peer-review

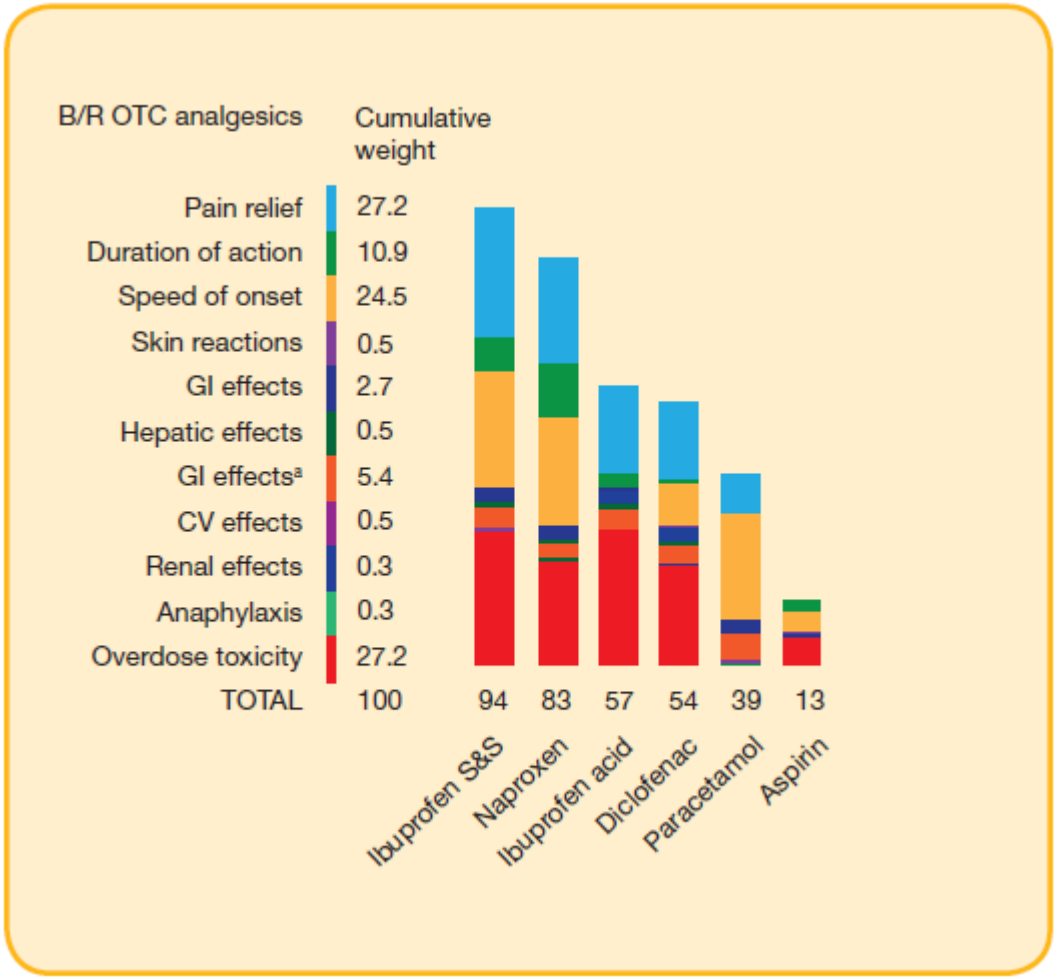

Figure 3 - Overall weighted preference scores with separate contributions shown for each effect. Longer segments for favourable effects indicate more benefit, while longer segments for unfavourable effects show greater safety

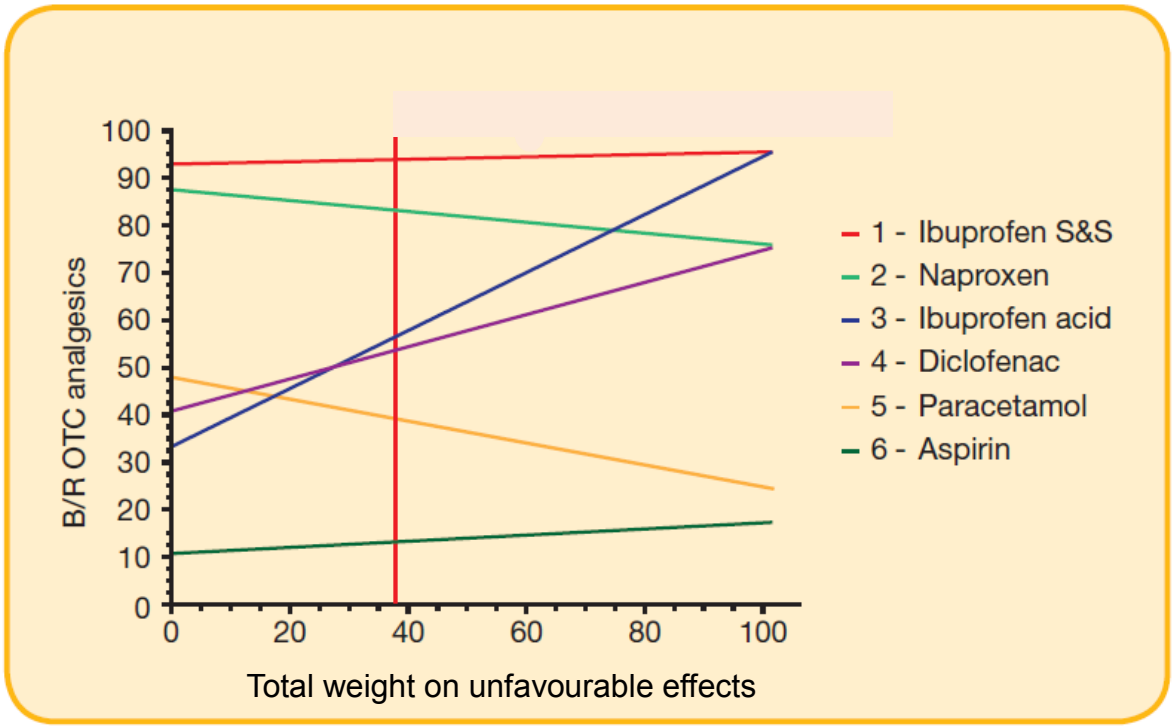

Figure 4: Sensitivity analysis for Unfavourable Effects

Table 1: Effects table highlighting the data inputs into the model. The first four rows are measured data, and the remaining rows are preference judgements.

Effects	Units	Ibuprofen acid	Ibuprofen S&S	Paracetamol	Diclofenac	Aspirin	Naproxen sodium
Favourable Effects							
Pain relief	%	48	63	33	45	20	55
Duration of action	hours	5.5	7	4	4.5	5	9
Speed of onset	mins.	55	27	30	45	50	30
Unfavourable Effects							
Adverse Reactions							
Skin reactions	N^{o}.	24	24	77	41	124	26
GI safety	Pref.	100	100	100	100	0	100
Hepatic safety	Pref.	100	100	0	100	30	50
Serious Adverse Reactions							
GI safety	Pref.	40	50	100	30	0	20
CV safety	Pref.	75	75	75	0	100	80
Renal safety	Pref.	100	100	100	100	100	0
Anaphylaxis	Pref.	50	50	100	50	0	50
Overdose Toxicity.	Pref	100	100	0	0	75	75

Note on units in the table: These are as presented in clinical studies. Some as percentages and others as actual numbers of incidents. Times as hours or mins (minutes), are mean times.

Table 2: Ibuprofen S&S compared to paracetamol. Green bars show the size of advantages of ibuprofen S&S, while red bars show the size of ad

Effects	Cumulative weight	Difference	Weighted difference	Total difference	
Overdose toxicity	27.2	100	27.2	27.2	
Pain relief	27.2	70	19.0	46.2	
Duration of action	10.9	60	6.5	52.7	
Speed of onset	24.5	11	2.6	55.3	
Hepatic effects	0.50	100	0.5	55.8	
Skin reactions	0.5	53	0.3	56.1	
GI effects	2.7	10	0.3	56.4	
CV effects	0.5	0	0	56.4	
Renal effects	0.3	0	0	56.4	
Anaphylaxis	0.3	-50	-0.1	56.3	
GI effects[a]	5.4	-25	-1.4	54.9	

Table 3: Summary of Main Outcomes of Assessment of Benefits and Risks of Over-the-counter (OTC) analgesics

Ibuprofen soluble 94 **FAVOURABLE EFFECTS** Shows best pain relief and speed of onset (27 minutes). Only naproxen shows longer duration of action. **UNFAVOURABLE EFFECTS** Safer than naproxen and aspirin for serious GI effects, which are about the same as diclofenac and worse than paracetamol. Both forms of ibuprofen are lowest for overdose potential.	**Naproxen 83** **FAVOURABLE EFFECTS** Longest duration of action (9 hr; compared with 7 hr for soluble ibuprofen, & 4hr for paracetamol. Speed of onset, 30 minutes, is about the same as soluble ibuprofen. **UNFAVOURABLE EFFECTS** The incidence and severity of serious GI effects is more than aspirin but less than the other drugs.	**Ibuprofen tablet 57** **FAVOURABLE EFFECTS** Pain relief is more than diclofenac, paracetamol and aspirin. Longer duration of action than diclofenac, paracetamol and aspirin **UNFAVOURABLE EFFECTS** This tablet form of ibuprofen shares with soluble ibuprofen the lowest potential for overdose.
Diclofenac 54 **FAVOURABLE EFFECTS** More than paracetamol and aspirin for pain relief and has a faster speed of onset than ibuprofen tablets and aspirin. **UNFAVOURABLE EFFECTS** Diclofenac has comparable serious GI effects with naproxen and less than aspirin. Low potential for overdose.	**Paracetamol 39** **FAVOURABLE EFFECTS** The 30-minute speed of onset of this drug and naproxen is slightly slower than soluble ibuprofen at 27 minutes, but at least 15 minutes better than any of the others. Better than aspirin for pain relief. **UNFAVOURABLE EFFECTS** It is the safest drug for serious GI effects, but has the highest potential for overdose.	**Aspirin 13** **FAVOURABLE EFFECTS** Speed of onset (50 min) comparable with ibuprofen (50 min*);* duration of action (5 hr), longer than paracetamol' (4hr) or diclofenac (4.5 hr). **UNFAVOURABLE EFFECTS** Aspirin has lower potential f than paracetamol for accidental or deliberate overdose.

The bold numbers are overall weighted preference values out of 100, which take into account available data for the effects, and judgements of the experts about the clinical relevance of the effects. They do not take account of contra-indications, interactions with other drugs, or other precautions. Figures given in the descriptions are averages; individuals may experience effects that are different from these averages.

6. Acknowledgments:

Professors Andrew Moore and Kim Rainsford are independent academic experts in pain and analgesics. Professor Lawrence Phillips is an expert on MCDA and had no influence on data input or interpretation. Dr Bernard Ng is an employee of RB Healthcare as were Dr Ozgur Sancak and Anne Crossley during the development of this manuscript.

Particular thanks are due to the members of the peer review panel for assisting with reviewing the quality of the data used, and the authors' interpretation of data that was entered into the model: Professor Laurie Prescott, Edinburgh University; Professor Nicholas Moore, Bordeaux University; Professor Angel Lanas, University Hospital Lozano Blesa, University of Zaragoza; Dr Brian Callingham, Department of Pharmacology, University of Cambridge; Professor Ingvar Bjarnason, Department of Colorectal Surgery and Gastroenterology, King's College Hospital, London.

We would also like to thank Robert Pawinski for managing the MCDA process and developing this manuscript.

Funding was provided by RBH Global Medical to an independent group of experts representing academia and industry. All authors had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Conflict of Interest:

KDR has been an independent expert witness for several regulatory bodies as well as being an independent consultant for several international companies that produce NSAIDs, including Reckitt Benckiser (RB). He has also given lectures at symposia sponsored by some of these companies.

RAM has received grant support from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake (2015). He has received honoraria from Omega Pharma (2016) and Futura Pharma (2016) for providing advice on trial and data analysis methods.

LP has facilitated decision conferences for several pharmaceutical companies comparing the benefit-risk profiles of prescriptions drugs, and has no conflict of interest regarding NSAIDs.

AC, OS and BN were all employees of RB Healthcare at the time of the development of this manuscript.

Footnote: The results of this study were presented in part to the meeting of the British Pharmacological Society, London, December 2014, and the 9th Congress of the European Pain Federation (EFIC), 2-5 September 2015, Vienna, Austria.

7. References

1. Rainsford, K.D., *Pharmacology and biochemistry of salicylates and related drugs*, in *Aspirin and Related Drugs*, K.D. Rainsford, Editor. 2004, Taylor & Francis: London. p. 215-366.

2. Rainsford, K.D., *Ibuprofen: Pharmacology, Therapeutics and Side Effects*, ed. K.D. Rainsford. 2015, Chichester: John Wiley & Sons Ltd.

3. Dale, O., et al., *Prevalence of use of non-prescription analgesics in the Norwegian HUNT3 population: Impact of gender, age, exercise and prescription of opioids.* BMC Public Health, 2015. **15**: p. 461.

4. EMEA, *Regulation (EU) No 1235/2010 of the European Parliament and of the Council of the European Union*. 2010: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf.

5. EMA. *European Medicines Agency: Procedure Management and Committees Support Division. PRAC Work Plan 2015 EMA/PRAC/794108/2013*. 2015; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2015/07/WC500189287.pdf.

6. Brass, E.P., R. Lofstedt, and O. Renn, *A decision-analysis tool for benefit-risk assessment of nonprescription drugs.* J Clin Pharmacol, 2013. **53**(5): p. 475-82.

7. Mussen, F., S. Salek, and S. Walker, *A quantitative approach to benefit-risk assessment of medicines - part 1: The development of a new model using multi-criteria decision analysis.* Pharmacoepidemiology and Drug Safety, 2007. **16**(S2-S15).

8. Nixon, R., et al., *A case study using the PROACT-URL and BRAT frameworks for structured benefit risk assessment.* Biometrical Journal, 2015.

9. Phillips, L.D., et al., *Is quantitative benefit-risk modelling of drugs desirable or possible?* Drug Discovery Today: Technologies, 2011. **8**(1): p. e3-e10.

10. Phillips, L.D., *Benefit-risk modeling of medicinal products: Methods and applications,* in *Benefit-Risk Assessment in Pharmaceutical Research and Development* A. Sashegyi, J. Felli, and R. Noel, Editors. 2014, CRC Press: Boca Raton, FL. p. 59-96.

11. Nutt, D.J., L.A. King, and L.D. Phillips, *Drug harms in the UK: a multicriteria decision analysis.* Lancet, 2010. **376**(9752): p. 1558-65.

12. Nutt, D.J., et al., *Estimating the harms of nicotine-containing products using the MCDA approach.* Eur Addict Res, 2014. **20**(5): p. 218-25.

13. Moore, R.A., et al., *Single dose oral analgesics for acute postoperative pain in adults.* Cochrane.Database.Syst.Rev., 2011(9): p. CD008659.

14. Moore, R.A., et al., *Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews.* Cochrane.Database.Syst.Rev., 2015(11): p. CD010794.

15. Catalyze, *HiView3 Software*. 2017, Catalyze Strategic Consultancy: http://www.catalyzeconsulting.com/software/hiview3/.

16. Dodgson, J., et al., *Multi-Criteria Analysis: A Manual*. 2000, London: Department of the Environment, Transport and the Regions, republished 2009 by the Department for Communities and Local Government.

17. Moore, R.A., et al., *Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain.* Pain, 2014. **155**(1): p. 14-21.

18. Hawkey, C., et al., *Endoscopic evaluation of the gastro-duodenal tolerance of short-term analgesic treatment with 25 mg diclofenac-K liquid capsules.* Aliment Pharmacol Ther, 2012. **35**(7): p. 819-827.

19. Rainsford, K.D., *Ibuprofen: Pharmacology, Therapeutics and Side Effects*, in *Ibuprofen: Pharmacology, Therapeutics and Side Effects*. 2012, Springer. p. 1-4.

20. Derry, S., P.J. Wiffen, and R.A. Moore, *Single dose oral diclofenac for acute postoperative pain in adults.* Cochrane Database Syst Rev, 2015(7): p. CD004768.

21. Einhorn, H.J., R.M. Hogarth, and E. Klempner, *Quality of group judgment.* Psychological Bulletin, 1977. **84**(1): p. 158-72.

22. Stephens, G., S. Derry, and R.A. Moore, *Paracetamol (acetaminophen) for acute treatment of episodic tension-type headache in adults.* Cochrane.Database.Syst.Rev., 2016(6): p. CD011889.

23. Moore, R.A., *Analgesic safety - myths, mysteries and misconceptions.* Int.J.Clin.Pract.Suppl, 2015(182): p. 24-27.

24. Moore, N., et al., *Does paracetamol still have a future in osteoarthritis?* Lancet, 2016. **387**(10033): p. 2065-6.

25. Moore, R.A. and N. Moore, *Paracetamol and pain: the kiloton problem.* European Journal of Hospital Pharmacy, 2016. **23**(4): p. 187-188.

26. Machado, G.C., et al., *Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials.* Bmj, 2015. **350**: p. h1225.

27. Saragiotto, B.T., et al., *Paracetamol for low back pain.* Cochrane Database Syst Rev, 2016(6): p. Cd012230.

28. da Costa, B.R., et al., *Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis.* Lancet, 2016. **387**(10033): p. 2093-105.

29. Kamath, A., *Paracetamol in osteoarthritis: NICE guidelines or not so nice.* J Postgrad Med, 2014. **60**(2): p. 212.

30. Wise, J., *NICE keeps paracetamol in UK guidelines on osteoarthritis.* Bmj, 2014. **348**: p. g1545.

31. FDA. *Consumer Updates - New Steps Aimed at Cutting Risks from Acetaminophen*. [WebContent] 2011; Available from: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm239747.htm.

32. Abramson, S., *Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.* 2013.

33. Tsai, W.C., et al., *Long-term frequent use of non-steroidal anti-inflammatory drugs might protect patients with ankylosing spondylitis from cardiovascular diseases: a nationwide case-control study.* PLoS One, 2015. **10**(5): p. e0126347.

34. Fayaz, A., et al., *Assessing the relationship between chronic pain and cardiovascular disease: A systematic review and meta-analysis.* Scandinavian Journal of Pain, 2016. **13**: p. 76-90.

35. Nüesch, E., et al., *All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study.* BMJ, 2011. **342**: p. d1165.

36. Arfè, A., et al., *Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study*. BMJ, 2016. **354**: p. i4857.

37. Gislason, G.H. and C. Torp-Pedersen, *NSAIDs and the failing heart.* BMJ, 2016. **354**: p. i5163.

38. Keeney, R.L., & Raiffa, H. , *Decisions With Multiple Objectives: Preferences and Value Tradeoffs.* 1976, John Wiley: New York:,.