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# Drug combinations in pain treatment: a review of the published evidence and a method for finding the optimal combination

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The evidence of the usefulness of drug combinations in pain management is reviewed and the problem of finding the optimal combination is presented. For post-operative pain, adding a non-steroidal anti-inflammatory drug (NSAID) or paracetamol to intravenous morphine is beneficial. Adding ketamine to intravenous morphine may be advantageous, but ketamine has a narrow therapeutic window. The combination paracetamol–NSAID is probably superior to either component alone. For post-operative epidural analgesia, combinations of low doses of a local anaesthetic, an opioid and adrenaline (epinephrine) are superior to single-drug regimens. There are virtually no data on the advantages of combinations over single drugs in neuropathic and chronic musculoskeletal pain. Adding NSAIDs or ketamine to opioids may be useful in cancer pain. Because of the enormous number of possible combinations, randomized controlled trials may fail to test the optimal combination. A stepwise optimization model that has been applied in clinical investigations is presented.

**Key words:** pain; drug therapy; combination; optimisation; direct search.

The rationale underlying the practice of combining drugs in pain management is based mainly on two considerations. First, single drugs do not always provide satisfactory pain relief: combining drugs that act at different receptors and on different pain mechanisms may enhance pain relief. Second, single drugs that provide satisfactory pain relief may cause, at the same time, unacceptable side-effects. Drug combinations may allow reduction in the amount of the single components to achieve the same analgesic effect with a lower incidence of side-effects. Clearly, this is true if the drug interaction is in favour of the analgesic effect, rather than of toxicity.

Despite the above considerations, combining drugs is still not always supported by the published evidence. Moreover, the optimal doses of each drug in most combination regimens remain unknown.

This chapter is divided into two parts. The first part gives an overview of the literature comparing drug combinations with single drugs. The second part analyses

the problem of optimizing therapeutic regimens and presents a method for optimizing drug combinations in clinical research.

## DRUG COMBINATIONS IN PAIN MANAGEMENT

This section does not intend to cover all combinations that have been investigated or may be used in pain management. Rather, it focuses on selected combinations for the management of acute post-operative, chronic musculoskeletal, neuropathic and cancer pain. Its aim is to evaluate the evidence that drug combinations are superior to single-drug regimens in clinical pain.

Medline and the authors' database were searched. Among the retrieved hits, only clinical investigations comparing a single drug with the combination of the same drug with one or more additional drugs were considered. Whenever systematic reviews were found they were used for evaluating the literature. Otherwise, randomized controlled trials, selected by the authors on the basis of a personal evaluation of their validity, are presented.

The main results of this review are summarized in Table 1.

### Postoperative pain

*Systemic analgesia*

*Opioids–NSAIDs*. The literature almost consistently shows either a morphine-sparing effect, lower pain scores or a decrease in side-effects when an NSAID is added to intravenous morphine.[1–8] One systematic review has analysed the effect of adding the

**Table 1.** Summary of results of the efficacy of drug combinations in pain management.

| | |
|---|---|
| *Acute post-operative pain* | |
| Adding NSAIDs to opioid | Mostly better analgesia and fewer side-effects |
| Adding paracetamol to opioid | Mostly better analgesia and fewer side-effects |
| Paracetamol–NSAID | Probably better than either component alone |
| Adding weak opioid to paracetamol | Questionable usefulness in minor surgery |
| Adding weak opioid to NSAID | Questionable usefulness in minor surgery |
| Adding intravenous ketamine to opioid | May be useful, but narrow therapeutic window of ketamine |
| Adding epidural opioid to local anaesthetic | Useful |
| Adding epidural local anaesthetic to opioid | Useful |
| Adding clonidine to epidural mixtures | Unclear benefit |
| Adding adrenaline to epidural mixtures | Useful at least for thoracic epidural analgesia |
| *Neuropathic pain* (peripheral nerve injury, post-herpetic neuralgia and diabetic polyneuropathy) | No data |
| *Chronic musculoskeletal pain* (fibromyalgia, low back and neck pain) | Sparse, inconsistent data on fibromyalgia, no data on low back and neck pain |
| *Cancer pain* | |
| Various combinations of opioids, NSAIDs, paracetamol and ketamine | Very limited data, possible usefulness of adding NSAIDs or ketamine to opioids |

NSAID: non-steroidal anti-inflammatory drug.

weak opioid codeine to the NSAID ibuprofen for post-operative pain.[9] Included papers considered minor surgery, mostly dental pain. The analgesic affect of ibuprofen was increased by only 8% by codeine, and adverse effects were increased.

*Opioids–paracetamol*. The addition of paracetamol to intravenous patient-controlled analgesia (PCA) with morphine decreased pain scores and increased patients' satisfaction.[10,11] The duration of PCA use was also decreased.[10] In an investigation on paediatric patients, paracetamol improved pain relief, reduced morphine consumption and reduced opioid-induced nausea and vomiting in a dose-dependent fashion.[12] In a systematic review, the combination of tramadol with paracetamol was superior to either component alone.[13] Three systematic reviews found that the addition of codeine to paracetamol improved pain relief.[14–16] In two of them[14,15], the combination was associated with an increased incidence of side-effects. Another systematic review found little objective evidence to support prescribing a combination of paracetamol and dextropropoxyphene in preference to paracetamol alone in moderate pain[17]: the difference in pain intensity between combination and paracetamol alone was only 7.3%.

*Opioids–ketamine*. When combined with morphine in a PCA regimen, ketamine decreased pain scores and the incidence of the side-effects.[18] The same effect was observed by using a continuous infusion of ketamine.[19,20] Interestingly, the area of hyperalgesia around the surgical wound was reduced by ketamine.[19] Conversely, two studies did not find any benefit of adding ketamine to morphine[21,22], but the sample size of one of them[21] may have been too low to detect significant differences. Ketamine caused an increased incidence of dreams in one investigation.[22]

*Paracetamol–NSAIDs*. One systematic review[23] found that the concurrent use of paracetamol and an NSAID was superior to paracetamol alone. However, no evidence of superior analgesic effect of the combination compared with the NSAID alone was found. Another systematic review[24] also found that the addition of an NSAID to paracetamol may confer additional analgesic efficacy. Unlike the former review, it concluded from the limited data available that paracetamol may enhance analgesia when added to an NSAID.

*Summary conclusions*. The addition of an NSAID or paracetamol to an opioid is probably beneficial, either in terms of analgesia, side-effects or both. Similarly, the combination of paracetamol with an NSAID is probably superior to either component alone. However, no study had enough power to analyse a possible increase in the incidence of rare serious adverse effects. For instance, it is unclear whether the association paracetamol–NSAID carries a higher risk of renal failure than either component alone. Moreover, the impact of combinations as routine analgesic regimens on overall costs is unclear.

The evidence supporting the addition of a weak opioid to paracetamol or to an NSAID is weak. Intuitively, moderate pain responding well to paracetamol or to NSAIDs is unlikely to benefit significantly from combining additional analgesics. Although most investigations indicate that adding ketamine to opioids is advantageous, negative studies have also been published. The narrow therapeutic range of ketamine, i.e. the small dose range that improves analgesia without causing side-effects, could explain the controversial results.

*Epidural analgesia*

*Adding opioids to local anaesthetics*. Lumbar epidural local anaesthetics alone are associated with a higher incidence of motor block than their combination with an opioid.[25] For thoracic epidural analgesia, adding an opioid to a local anaesthetic probably improves pain control.[26,27] The incidence of side-effects is either decreased[28], unchanged[26] or even increased.[27] The effect of adding an opioid to a local anaesthetic probably depends on the type and dose of opioid used. The addition of low concentrations of fentanyl (i.e. 2 μg/ml) to a bupivacaine–epinephrine thoracic epidural infusion strongly improved analgesia without increasing side-effects in a cross-over study.[26]

*Adding local anaesthetics to opioids*. Studies have shown either a benefit[29] or no advantage[25] of adding a local anaesthetic to pure opioid solutions. It is likely that local anaesthetics do not confer benefits when added to high-dose opioids because high doses may provide adequate analgesia even when used alone. However, several dose-dependent side-effects may result from opioid administration.[30] Most studies are underpowered to analyse whether opioids alone are associated with more respiratory depression than mixtures of low-dose opioids with local anaesthetics. Moreover, pathophysiological data support the superiority of local anaesthetics to opioids in reducing cardiovascular and respiratory morbidity, as well as the duration of post-operative paralytic ileus.[31] The authors believe that combinations of low doses of local anaesthetics with opioids should be preferred to opioids alone for post-operative pain relief.

*Adding clonidine to epidural mixtures*. The addition of clonidine to a bupivacaine–fentanyl infusion produced improvement in analgesia, but also a higher incidence of hypotension.[32,33] However, better pain relief without increase in side-effects was produced by the addition of a single injection of clonidine to caudal[34] or epidural[35] bupivacaine. Perhaps clonidine could have a role in lumbar epidural analgesia: the concentration of local anaesthetic may be reduced by the additional use of clonidine, with possible decrease in the incidence of motor block. Studies on this issue are lacking.

*Adding adrenaline (epinephrine) to epidural mixtures*. The addition of adrenaline (epinephrine) to mixtures of opioids with local anaesthetics has proven beneficial for thoracic epidural analgesia in most literature.[36–39] Therefore, the limited use of adrenaline (epinephrine) in current practice seems unjustified.[40] Results concerning lumbar epidural analgesia are less consistent and require further investigation.[29,41–44]

*Summary conclusions*. Combinations of low doses of a local anaesthetic, an opioid and adrenaline (epinephrine) are superior to single-drug regimens. The role of clonidine is still unclear.

## Neuropathic pain

The literature was searched for all possible drug combinations for neuropathic pain. The focus was set on peripheral nerve injury, post-herpetic neuralgia and diabetic polyneuropathy. Unfortunately, the authors were able to identify only one study comparing a combination with a single-drug regimen: the addition of the neuroleptic

fluphenazine to the antidepressant amitriptyline did not improve analgesia in patients with post-herpetic neuralgia.[45]

*Summary conclusions*. The literature on drug combinations in neuropathic pain is virtually non-existent. Although we cannot rule out that our search may have missed some randomized controlled trials, there is certainly a need for research on drug combinations in this difficult pain condition.

## Chronic musculoskeletal pain

The focus of the search was on unlimited combinations of analgesics in fibromyalgia, low back pain and neck pain. Additionally, specific searches were conducted on combinations of NSAIDs, paracetamol and opioids.

No study on drug combinations in neck or low back pain was found. In the light of the enormous medical, social and economic implications of these pain syndromes, such absence of data is disconcerting.

In fibromyalgia, the addition of ibuprofen to the muscle relaxant cyclobenzaprine improved morning stiffness.[46] A combination of naproxen with amitriptyline was slightly, but not significantly, better than amitriptyline alone.[47] Combinations of NSAIDs with benzodiazepines were investigated in two studies. The combination of tenoxicam with bromazepam was only marginally better than tenoxicam alone, but not better than placebo.[48] The combination of ibuprofen with alprazolam produced a more pronounced clinical improvement than either drug alone.[49]

*Summary conclusions*. Because of the extreme paucity of evidence, the authors cannot make any conclusion on the usefulness of combinations in chronic musculoskeletal pain.

## Cancer pain

Search was conducted on the following drug combinations: opioids–NSAIDs, opioids–paracetamol, NSAIDs–paracetamol and opioids–ketamine. Very few studies were found.

The addition of diclofenac to intravenous PCA with morphine reduced morphine consumption.[50] There was a trend for reduced pain scores, which did not reach statistical significance. Two placebo-controlled studies found that adding ibuprofen to the combination oxycodone/paracetamol[51] or methadone[52] significantly decreased pain scores without increasing side-effects. Conversely, adding codeine to diclofenac did not affect pain scores.[53]

The use of low doses of ketamine reduced morphine consumption and pain scores, but a dose-dependent increase in central side-effects was observed.[54,55]

*Summary conclusions*. The limited published evidence suggests that adding NSAIDs or ketamine to opioids may be useful. Randomized controlled trials on other combinations are lacking.

## FINDING THE OPTIMAL DRUG COMBINATION

### The problem of identifying the optimal combination

Generally, drug combinations are investigated by comparing two or more groups, each receiving a different combination. However, this approach is challenged by a serious problem: the number of possible combinations. If we combine two different drugs and analyse two doses for each drug, $2^2 = 4$ different combinations exist. However, if the therapeutic range of the drugs under investigation is wide, we may want to analyse a larger number of different doses, for example, five. In this case, we would have to analyse $5^2 = 25$ different combinations. If we want to add an additional variable, for example, another drug, or the time interval between the doses, the number of possible combinations increases to $5^3 = 125$. Therefore, only a small proportion of all possible combinations can be investigated in a randomized controlled trial. Such a trial allows conclusions pertaining only to the combinations analysed, and the optimal combination may not be among those tested.

Thus, there is a need for methods to identify optimal combinations of therapeutic regimens. Actually, optimization models have existed for a long time and are commonly applied to real economic problems.[56] Conversely, despite its great importance, the problem of optimizing therapeutic regimens has received very little formal attention in medicine.[57]

In the present section we present an optimization method that can be applied to clinical research. The basic principle of this model is derived from methods that have been used extensively in economics. To our knowledge, only two human clinical studies using this method have been published, both by our research group.[58,59]

### The direct search optimization method

The optimization method presented is named 'direct search'. The principle is simple. The optimum is searched for stepwise. Initially, few combinations are tested. On the basis of the results obtained, new combinations are identified stepwise, and investigated, until the optimal one is reached. Basically, the information obtained by the analysis of the combinations at each step is used to move away from the 'bad' combinations in the direction of the 'good' ones, towards the optimum. In this way, it is not necessary to explore all possible combinations.

In the following sections, three direct search methods are presented, from the basic one to the latest development in clinical research.

#### *Simplex method*

The 'simplex' method[56] has been used mainly in mathematical and industrial problems and is presented here because it easily illustrates the principles of optimization models (Figure 1). Its main disadvantage for applications in clinical research is the excessive weight given to each combination. Measurements performed in a clinical setting are usually characterized by a large variability. Therefore, a certain combination can perform as the worst one merely as a result of chance. Because the step direction is given by the position of the worst combination (Figure 1), a wrong estimation would direct the procedure towards a wrong point.

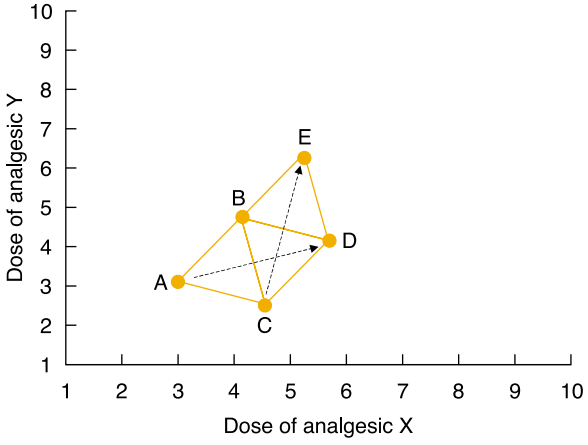


**Figure 1.** The simplex method for optimization. For a problem of $n$ variables, an initial complex of $n + 1$ empirically chosen combinations is analysed. In the example illustrated, two analgesics, X and Y, are combined, i.e. $n + 1 = 3$ combinations are initially analysed (combinations A, B and C). These combinations have to form the vertices of an equilateral triangle. After analysing these combinations, the one characterized by the worst analgesic effect (in this example combination A) is discarded. The basic principle of the method is to move away from the 'bad' combinations in the direction of the 'good' ones. A new combination, D, is determined by reflecting the triangle A–B–C on the axis B–C of the initial complex (i.e. the axis of the two 'good' combinations). Combination D of the new complex B–C–D is analysed in an additional group of patients, without the need for re-testing combinations B and C. The worst combination of the complex B–C–D (i.e. combination C) is discarded and the new combination E is determined. The procedure is stopped when no further improvement in the therapeutic effect is obtained.

*Partition method*

In order to overcome the problem described above, Berenbaum developed the 'partition' optimization model, which he then applied to a study of chemotherapy in animals.[57] We implemented this method in a clinical study to optimize a post-operative epidural regimen.[58] The search converged to a bupivacaine dose of 9–13 mg/hour, a fentanyl dose of 21–30 μg/hour, a clonidine dose of 0–5–μg/hour and an infusion rate of 7–9 ml/hour.

Figure 2 illustrates an example of an optimization step using the Berenbaum model. The main rationale is to avoid the excessive weight given to the worst combination by the simplex method (Figure 1). This minimizes the potential bias resulting from the large variability which characterizes clinical research.

The method provides a multiple regression model to deal with the occurrence of unacceptable side-effects.

More details on the method can be found in previous literature.[57,58,60]

*New partition method*

In a recent optimization study[59], we analysed a morphine–ketamine regimen for PCA. The procedure converged to a morphine : ketamine ratio of 1 : 1 and a lockout interval of 8 minutes. The median bolus doses of both drugs were 0.9–1.8 mg, reflecting the well-known high interindividual variability in analgesic consumption. For that study, we developed a new partition method that addresses some limitations of the original Berenbaum's approach.

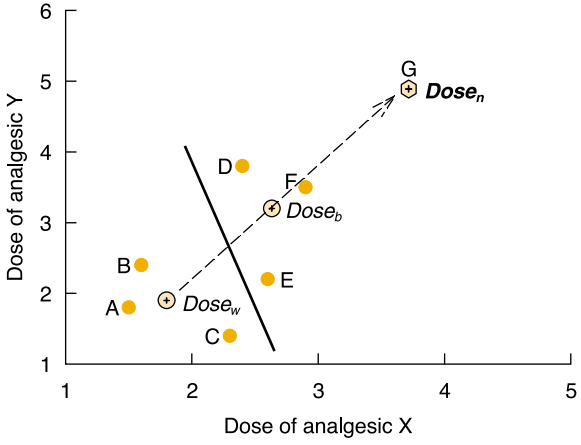


**Figure 2.** Berenbaum's partition method for direct search. The main rationale is to avoid the excessive weight given to the worst combination by the simplex method (Figure 1). In the example illustrated, a complex of six combinations A–F of two analgesics, X and Y, is represented. These combinations are ranked from the best to the worst one according to their analgesic effect, for example, the mean pain score. It is important to note that differences in pain scores do not need to be statistically significant, so that it is not necessary to analyse large sample sizes. Once the combinations are ranked they are 'partitioned' into two equal subgroups: the worst (A–B–C) and the best (D–E–F) combinations. The continuous line divides the two subgroups. Then the mean doses of the combinations of each subgroup are calculated, and two virtual combinations, i.e. the centroid of the worst three and the centroid of the best three combinations, are identified ($Dose_w$ and $Dose_b$, respectively). The new combination, G, of the optimization procedure is calculated by the equation $Dose_n = Dose_b + \alpha(Dose_b - Dose_w)$, where $\alpha$ is a positive number (in this case $\alpha = 1.3$). In this way, the relative position of the three worst combinations in the ranking does not influence the direction of the next step because the mean of the doses is considered for calculating the new combination G. Assuming that the worst of the six initial combinations in our example is A, this combination is discarded and the new combination G is tested on an additional group of patients. The above ranking and partition procedure is repeated on the new complex of six combinations (B–G), whereby five (B–F) had been tested in the previous phase.

First, the Berenbaum's algorithm did not provide guidelines for choosing the number of combinations per complex (six in the example of Figure 2) and the number of patients per combination. Choosing excessively low values of these parameters would reduce the time necessary to test a complex but does not necessarily reduce the number of steps required to reach the optimal combination. In fact, the correct search direction may be deviated from by measurements coming from outlying patients, and more steps would be required to reach the optimal point. On the other hand, a large number of combinations per complex and a large number of patients per combination may provide the correct search direction – but at the cost of an expensive study. Based on a simulation procedure performed on data from the previous investigation[58], we determined that the optimal number of combinations per complex and the optimal number of patients per combination are eight and six, respectively.

Second, partitioning the complex by cutting the ranked list at its half (i.e. creating two equal subgroups, Figure 2) is arbitrary. For instance, the worst combination of the 'good' subgroup and the best combination of the 'bad' subgroup could be characterized by very similar and clinically indistinguishable pain scores. In this case, it would be more productive for the optimization procedure if these two combinations belonged to the same subgroup because a more reliable calculation of the centroids of the 'good' and 'bad' subgroups (Figure 2) would result. We achieved

this by partitioning the complex using a probabilistic model. The effect of this different approach is illustrated in Figure 3. The specific procedure is described in detail in the published paper.[59]

Third, two combinations whose average pain scores differ from each other markedly may be characterized by distributions of pain scores that significantly overlap. In this case, ranking the combinations based on the average pain scores may reflect a wrong estimation of their relative analgesic efficacy. To minimize this problem we ranked the combinations by considering the distribution of pain scores, rather than just the average value. Details of the specific procedure can be found in the paper.[59]

*Limitations of the direct search method*

The expectation of an improvement in the outcomes during the study period may produce an observer bias. This can be minimized by blinding patients to the stage of the optimization procedure and defining outcomes that depend as little as possible on the observer's evaluation.

The study may lead to a local minor peak of the response surface. This is like reaching a minor peak of a mountain without knowing that there is a higher one. The search gets 'trapped' in the minor peak and the investigator is convinced that the optimum has been reached because further steps either lead to toxicity or do not produce improvement in the variable to be optimized. This is a theoretical problem that could be addressed by starting the search from two different points and seeing

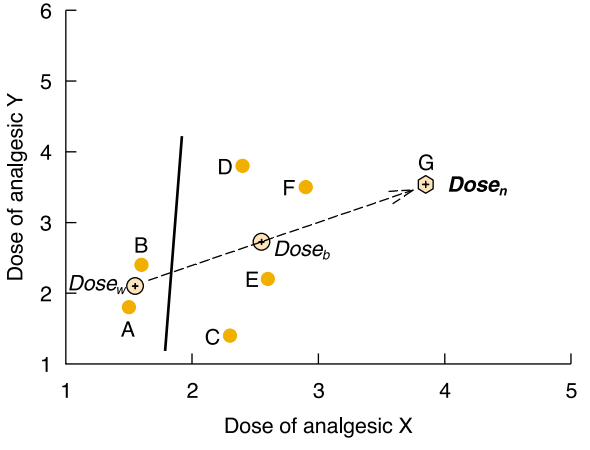


**Figure 3.** In the example illustrated here the model proposed by Berenbaum was improved by choosing a more rational approach to partition the complex into the 'good' and 'bad' subgroups. The same initial six combinations (A–F) as in Figure 2 for the starting complex were used to allow direct comparison. The ranking of the combinations A–F according to the pain scores allocated combinations C and B as the 4th and 5th ones, respectively. According to the original method by Berenbaum (Figure 2), the complex would be partitioned into two equal halves, so that both combinations C and B would belong to the 'bad' subgroup (Figure 2). However, we assume that the mean pain score of combination C is very close to that of combination E, so that the difference would be clinically indistinguishable. Conversely, the pain score of combination C is much lower than the pain score of combination B. The probabilistic model implemented here would allocate combination C to the 'good' rather than to the 'bad' subgroup, unlike the Berenbaum method (Figure 2). This changes the direction of the search procedure, as indicated by the different position of the new combination, G compared with Figure 2.

whether the two independent procedures converge to the same result.[60] However, this would require more resources. A pragmatic approach is to define a clinically meaningful optimum and stop the search when this result has been reached and cannot be further improved.

In the absence of validation, there is no real evidence that the optimum has been reached. A possible way of validating the results is to re-test and compare the best and the worst combinations of the whole procedure in a randomized double-blind fashion. However, this raises the ethical problem of using a 'bad' combination in patients. In our studies[58,59]we re-tested two of the combinations that were included in the final subgroup of best combinations. In both studies, these combinations were ranked again in the best subgroup after re-testing.

As for all investigations that analyse small sample sizes, the incidence of rare adverse effects cannot be quantified.

### The role of optimization methods in clinical research

Because of their nature, results of optimization studies cannot be considered conclusive. Rather, they may identify the range of the optimal components of a therapeutic regimen: the wide range of possibilities, giving rise to an enormous number of possible combinations, is 'narrowed' to a small range of potentially useful combinations which can then be analysed by randomized controlled trials. Therefore, optimization studies complement randomized controlled trials rather than being an alternative to them. Furthermore, prospective observational studies, investigating the best combinations on samples of large size, should be carried out to assess the incidence of rare complications. We believe that optimization procedures are more scientifically based than pure empiric selection criteria of drug combinations and should therefore be preferred to the latter.

## SUMMARY

In acute post-operative pain, various combinations of NSAIDs, paracetamol and opioids are superior to single drugs in terms of analgesic effect and/or side-effects. However, there is mostly no evidence that rare severe adverse effects are not increased by drug combinations. Adding ketamine to intravenous morphine for post-operative pain may be beneficial, but the challenge is to find the useful ketamine dose that does not cause side-effects. For epidural post-operative analgesia, combinations of low doses of a local anaesthetic, an opioid and adrenaline (epinephrine) are superior to single-drug regimens. The role of epidural clonidine is still unclear. There is a disappointing lack of data on the advantages of drug combinations over single drugs in neuropathic and chronic musculoskeletal pain. Based on very limited data, adding NSAIDs or ketamine to opioids may be useful in cancer pain. Other combinations are unexplored.

The problem of how to find the optimal combination of therapeutic regimens has received very little attention in medicine. Because of the enormous number of possible combinations, randomized controlled trials may fail to test the optimal combination. The direct search method is a stepwise optimization procedure that has been used in two clinical investigations on post-operative analgesia. A wider use of optimization methods in clinical research is desirable.

**Practice points**

- in acute post-operative pain, various combinations of NSAIDs, paracetamol and opioids should be preferred to single-drug regimens after major surgery. In minor surgery, drug combinations should be used only when single drugs provide inadequate pain relief
- there is some – although equivocal – evidence that adding ketamine to systemic opioids is beneficial in post-operative pain
- combinations of low doses of local anaesthetics, opioids and adrenaline (epinephrine) are superior to single-drug regimens in epidural post-operative analgesia
- the rationale underlying the use of drug combinations applies also to neuropathic and chronic musculoskeletal pain, but this practice is accompanied by an almost complete lack of published data
- the very limited data on cancer pain suggest that adding NSAIDs or ketamine to opioids may be beneficial
- randomized controlled trials allow conclusions pertaining to the specific combinations analysed. Because of the large number of possible combinations of a therapeutic regimen, the optimal combination may not be tested

**Research agenda**

- randomized controlled trials, performed on large patient populations, are needed to assess the cost/benefit ratio of drug combinations and their safety in terms of rare adverse effects
- research on drug combinations may offer a perspective of better treatment of cancer, neuropathic and chronic musculoskeletal pain
- existing optimization methods should be used more widely in clinical research
- the currently available optimization methods may be improved by methodological studies

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