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Review Article

The Management of Chronic Pain: Investigation of Strategies for Combining Drug Therapies for Optimal Efficacy, Safety, and Cost-Effectiveness

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ABSTRACT

Chronic pain is now one of the significant health care issues. Nowadays, its management is a significant problem in terms of the quality, of life for the improvement of the social and relational activity. The result of the individual quality life under, chronic pain condition is a decrement of the average life condition and increase of the cost for its management.

The measurement of the outcomes is efficacy, safety, and cost-effectiveness, can give an improvement in patients care. It can give rise to the interest of the participants to take part in the trail. When the trail starts the investigators should involve patients and let them be part of the research. They could work together on the research topic development and so even on outcome assessment. Public and patient involvement PPI could improve recruitment because it implements the ethical design. The approval could be straightforward due to their ownership.

Keywords: Paracetamol, Tramadol, Efficacy, Intervention.

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INTRODUCTION

The research aims to assess the efficacy, the safety and the cost-effectiveness of oral paracetamol and tramadol oral against oral tramadol only. Patients and public services will benefit from this research thank to the improvement of quality life directly and thank the reduction of cost provision in the longer term. Carers can receive information about the differences between the treatments in a long prevision [1].

Is the combination of oral paracetamol and tramadol tablets against tramadol tablets only like control, more effective and safer for the treatment of chronic pain? What is the cost-effectiveness assessment?

Patients

Further, socioeconomic, and psychological patients' features may be considered to assess their influence on the pain management strategies such as:

- Male and female indifferently;
- More than 18 and less than 75 years old;
- Excluded by the ethnic minority for ethical reasons;
- Affected by chronic pain.

Intervention

Oral paracetamol 325 mg and oral tramadol 37 mg, 5 mg 2 tablets four times daily.

Comparison

Oral tramadol 50 mg, 2 tables four times daily.

Outcome

Efficacy is the primary outcome (pain reduction assessment executed by pain intensity measurement, recovering physical functions and quality of life evaluation: like psychosociological and behavioural functions). Safety is the secondary outcome (incidence of ADRs). The overall evaluation of the combined therapy (paracetamol and tramadol) against tramadol only is the central question of this study. Moreover, cost-efficacy evaluation is an additional outcome [2].

Time

The entire follow-up time of the trial is 135 days, as the chronic pain median interval is 135 days (as chronic pain range is from 90 to 180 days).

The two possible experimental, analytic studies are: the randomised controlled parallel groups trail or randomised prospective crossover trial.

The randomised controlled double-blind, parallel groups, (ratio 1:1), is the most appropriate type of clinical study. Its aim is comparing the efficacy, the safety, and the cost-effectiveness of the treatments against chronic pain. The clinical assessment measures, thank (ratio 1:1), can give an evident appraisal and so a balance the differences between the intervention and the comparison. Many participants, in this study, could generate a loss of data derived by the discontinuation and, consequently, by incomplete outcome measures [3].

On balance, a randomised crossover prospective trial is not the most appropriate to measure the level of pain. As the washing period would damage the assessment of the parameters, invalidating the results. Further ethical consideration should increase the doughs to use this study; the interruption of the therapy could result in a lack of pain relief (beneficence ethic principle) during the experimental treatment. The washing period would increase the complexity of the analysis for the final assessment in this case. Moreover, in this type of study, the investigators could directly evaluate the outcomes of the small sample of participants. The restricted number of patients necessary for the assessment reduces the cost to lead this type of study and the overall study management.

Defining the study population and setting

The autonomy, the justice, the beneficence, and the non-maleficence, are the essential ethical criteria to write the protocol. The eligibility criteria set the protocol on these ethical principles. Chronic pain and health status are related to the assessment of vulnerability. Additionally, the following section mentions age, physical incapacity, and psychological conditions for the assessment of the eligibility [4].

The population under study should be male and female patients indifferently, aged more than 18 and less than 75 years old. No patient should belong to any ethnic minority. No patients in assessment can take part in the study without an appropriate ethical assessment of the incapacity condition (justice). Pregnant and breastfeeding women cannot take part in the trial (non-maleficence). Socioeconomic and psychological conditions can be determined for the protocol approved by the ethics committee (justice). Physical impairment assessment, chronic pain assessment and the overall status of health evaluation led to the appropriate patient evaluation for the participation (justice) [5].

Inclusion criteria:

Proof of chronic pain, willingness to sign the informed consent previously (autonomy), chronic pain relief measurability, personal feature limits, (e.g., age, maternity, or breastfeeding), (non-maleficence).

Exclusion criteria:

Abnormal clinical conditions, liver and renal function assessment, hypertension, vascular disease, psychiatric disorder (justice), and patient in therapy with other agents that may interact with CYP 450, incapability to guarantee the follow-up, severe socioeconomic conditions (justice) [6,7].

First approach:

Patients affected by chronic pain can be identified as it follows: by the International Classification of Diseases ICD-11 realised by the World Health Organization.

The type of chronic pain differentiates them in seven ways-

Chronic primary pain:

Persistent type of pain in different unrelatable parts of the body.

Chronic cancer pain:

Pain due to cancer.

Chronic posttraumatic pain:

Post trauma or surgery over three months.

Chronic neuropathic pain:

Pain due to nervous system damage.

Chronic headache and orofacial pain:

Pain from head or face.

Chronic visceral pain:

Pain from an internal organ.

Chronic musculoskeletal pain:

Pain from the bones, the muscles, and the joints.

This assessment identifies the patients by the origin and location of pain.

The recruitment is based on a test development to the origin and location of the illness. This identification of the stakeholders is based on the participants' relevant information, on monitoring and evaluating them. By origin of the illness, the absence of qualification of the level of pain, at the baseline, limits the assessment during the follow-up interviews [8].

Selection 1:

It is based on the clinical information collected on the patients and on the eligibility criteria. This information is fundamental to the allocation process. Moreover, the diagnosis can confirm the presence of chronic pain in patients selected. There is no analysis of the level of pain at the baseline.

This approach limits the identification of the disease progression during the treatment because it gives an evaluation of chronic pain based on its origin and quality. Eligibility criteria and the respect of participants' autonomy (informed consent previously signed) are necessary to start the selection procedure. This relevant information about the stakeholders is necessary to develop recruitment appropriately.

Second approach:

Patient's identification, by Mc Gill pain questionnaire, quantifies the severity and intensity of chronic pain identifying the patients' features.

"Recruitment Trial Design and Protocol Development study by Grant D. Huang et al., 2018" Can lead the recruitment methods. It identifies and engages all stakeholders as equal partners in the study process. Recruiters collect the data between the participants and ensure the validity of the question to the stakeholders and for the eligibility criteria.

Selection 2:

It is based on the calculation of the severity of the injury, on disease progression measurement, on eligibility criteria (the evaluation procedure guarantees the allocation and follow-up) and on samples homogeneity.

This second approach qualifies the scale of the severity of the injury. In this way, the qualification of the efficacy and safety of the intervention against the control is guaranteed from the baseline. The recruitment based on the engagement of all the stakeholders' qualification gives the chance to give to data the same scientific weight in both the harms of the trail. Eligibility criteria do not give only the ethical respect for the participants, but even the appropriate appraisal of the personal feature for trial design and protocol approval. This approach gives an accurate appraisal of the illness without taking into consideration the site of the illness.

Outcome measurement

The primary outcome is efficacy. It is measured by disease progression thank the continuous pain measurement. The study aims to define the pain the relief and unwanted side effects during the treatment in the two harms of the trial; the chronic pain can be identified and classified by the international classification of disease ICD-11 classification test by the World Health Organization; or by Mc Gill pain questionnaire for chronic pain assessment. The intervention measurement and comparator measurement are disease progression [9,10].

• The advantage of the first approach is the study can define the efficacy of the treatment in the site of injury or its pathology type, e.g., positive effect against multiple sclerosis-like a type of spinal pain. The disadvantage of this approach is: the measurement of the primary outcome as free progression disease is easily not valuable. As also, the interaction between the level of pain measurement and the illness site.

• The advantage of the second approach is the measurement of the pain level which is tightly related to the outcome assessment. Mc Gill pain questionnaire is a useful tool for the free progression of disease measurement against the intervention and comparator assessment. The disadvantages of the second approach are the appraisal of the efficacy as primary outcome without considering the illness site.

The safety is the secondary outcome, is realised on ADRs collection, identification, and evaluation in both the harm of the trail compares

their incidence values. The ADRs assesses rate safety. An appropriate assessment of the drug interaction in the intervention derives the pharmacokinetic and the pharmacodynamic drug profile. The primary outcomes can be measured weekly from the baseline of the trial until the end. It assumes that the median duration of the treatment is 135 days. Covariate measurements are the level of pain site, the origin of the illness; the psychological conditions can influence pain management.

Cost-effectiveness

The difference between the two harms of the randomised controlled trial sets the cost-effectiveness assessment. It assumes that the median duration of the treatment is 135 days [11-13].

The daily cost of the paracetamol and tramadol oral therapy is 2,27 £/60=x × 8 tables daily=0,30 £; for the maximal extension of the therapy is 135 days the price is 40,5 £.

The daily cost the oral of tramadol therapy is 1,09 × 8 tables daily=8,72 £; for the maximal extension of the therapy is 135 days the price is 1.177,2 £.

On balance, the price of the therapy for the whole maximal duration is lower in the intervention than in the comparison.

The epidemiological study reports an effect reduction, but tolerance increase for paracetamol and tramadol combined treatment.

The tramadol effect reported on: "Tramadol for neuropathic pain in adults" Cochrane library "At least 50% pain intensity reduction was reported in three studies (265 participants, 110 events)".

Quality-adjusted life years have an impact on therapy management. In conclusion, the intervention is better than the comparator.

The primary intervention is the association between oral paracetamol 325 mg and oral tramadol 37, 5 mg 2 tablets four times daily.

The measure of the efficacy is set on the disease progression. The appraised parameters are:

• The absolute risk, like absolute risk reduction. (It is the probability that an event can occur.) This value shows the reduction of the pain thanks to the intervention.

• The appraisal of the confidence interval CI can assess the interval containing the range of values related to the population.

The appraisal of the safety, like the secondary outcome, is set on the incidence of ADRs in the two groups, for intervention and comparator difference assessment. The assessment starts right after the baseline, to decide the trend of the pain intensity and ADRs during the follow-up period, once weekly, as it has been told yet. It can appraise the disease progression during the treatment from the baseline until the end of the trail. As told before, pharmacokinetic (metabolism of tramadol to action on cytochrome P450, subtype 2D6) and pharmacodynamic evaluation would implement the scope of the research assessing the drug interactions for safety evaluation. Furthermore, physiological assessment can be a valid method to assess the behavioural impact on drug evaluation and therapy cost management.

Comparator:

Oral tramadol 50 mg 2 tables 4 times daily. (The comparator is standard care against chronic pain.)

Relative risk value, like relative risk reduction value, is the absolute ratio difference between a group and the other. This value shows the difference in pain reduction in the groups. It explains the measurement of disease progression difference between the two groups.

Furthermore, the confidence interval CI sets the range of data that give a plausible value. The comparison evaluates pain relief like disease progression. These are the objective responses identified by Mc Gill pain questionnaire. The results of the comparator values against the intervention would be the outcomes analysis. The comparison of ADRs can be measured thank to the incidence of each ADRs in the two harms of the trial. The implement of the assessment of the comparator uses the same parameters given in the intervention groups for ADRs evaluation. It has been underlined yet that a psychological appraisal could improve the assessment.

The level of pain at the baseline of the study is, indeed, a primary issue. It is essential to evaluate the difference between each patient. The characterisation of the origin of covariates in patients with chronic can be set on the International Classification of Diseases ICD-11 realised by the World Health Organization. Furthermore, the patients' psychological features may be considered as covariance as they influence pain management.

REVIEW OF LITERATURE

An important covariate measurement is the diagnosis of the illness. It is used to assess the site and type of injury. Level of pain measurement, by the McGill pain questionnaire, can evaluate the efficacy of the treatment by assessing pain decrement. It outlines the outcomes of the study. Symptom checklist-90 revisited, or CL profile of mood states tests are the further tools to assess psychological variation of the pain and its management during the treatment. The variation is useful to appraise the differences between illness characterisation, level of pain and psychological influence. The appraisal of the ADRs in the groups of the trail is a critical covariate assessment as they affect the competence of the treatment and the cost-effectiveness influencing quality of life. These last items are confounding elements.

Data collection details:

Case report forms can precisely collect data for the assessment of efficacy and safety. An additional assessment of covariate could be done by pain disability index PDI and by the psychological test mentioned.

It is necessary to collect these values to have a clear assessment of the data as they could derive from the original propose. In other words, covariates qualify the deviation from the standard value. For this reason, it assessed:

• The type and the site of chronic pain as well as its level

• The psychological variables that affect the treatment

• The ADRs assessment.

Minimising bias

The blinding procedure starts simultaneously at the beginning of the intervention and the beginning of the comparator administration. It is necessary, during the collection of data, to ascertain their fatefulness. The blinding procedure is useful to minimise measurement bias. Patients report outcomes by the tests. The possibility that the treatments can be a double-blind study strengthens the minimisation of observational bias, during trial conduction. 12 The observers and the participants' awareness can alter the detection of the data overestimating or underestimating the efficacy and the severity of ADRs for the appraised treatment.

Consequently, the data collected and so the results can occur in random errors. It results in a deviation from the real outcome values due to a reduction of the precision. Another type of observational error (or measurement error); it is the systematic error introduced in the trial for inaccuracy. It reduces statistical accuracy. As it has been underlining yet, the awareness can result in performance and detection bias that can alter the intervention evaluation. Exclusion/attrition bias results in

the withdrawal of participants. All these elements are to be set clearly in the blinding/masking section of the protocol.

Sample size considerations

The following two citations from: "Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies" give the dimension of the phenomenon chronic pain.

• "Chronic pain affects between one-third and one-half of the population of the United Kingdom, corresponding to just beneath 28 million adults, based on data from the best available published studies. This figure is likely to increase further in line with an ageing population."

• "The prevalence of chronic pain, derived from 7 studies, ranged from 35.0% to 51.3% (pooled estimate 43.5%, 95% CIs 38.4% to 48.6%)".

The population of appraised is 28 million. The sample size is 385 a group; the margin of error is 5%, the confidence interval CI 95%, the sample proportion is 50% (ratio 1:1). The power is 95%, as the confidence of values estimates. The sample size calculation includes the power, the level of significance and effect size. The biggest possible sample size and the most meaningful is the one given in this calculation. It is the most appropriate to detect the difference of outcomes during this randomised controlled trial RCT because it can confirm the power of a binary hypothesis test if the test rejects the null hypothesis when the alternative hypothesis is true.

The following tests assess chronic pain. These tests can implement the collection of data on the level of sufferance and so, during the trail, the measurement of the parameters. The participants would be chosen to thank a diagnosis that confirms the presence of chronic pain. Information will be collected in the following questionnaires like qualitative studies.

Mc Gill pain questionnaire evaluates the pain in patients by factors like: "quality, location, exacerbating, and ameliorating factors" as it is reported in the article "Assessment of patients with chronic pain". It can determine the effectiveness of an intervention. The following questions derive from Mc Gill pain questionnaire:" What does your pain feel like?; How Does your pain Change with Time?; How Strong is your pain?". Each question is related to a response associated with a description for group: like, firstly (temporal) or (constrictive pressure) and secondly to a descriptive factor (flickering) for question 1; to a question and then to a response like (rhythmic, periodic, intermittent) for question 2; and to a question and then to a response like (horrible) for question 3. Each question corresponds to one answer only. The answer corresponds itself to a number which generates the total pain scores. They generate the pain level score from a minimal pain level score of 0 to a maximum pain level score of 78. The test result interpretation is the higher the exponential pain rate is the more important is the pain condition [14].

Ethics, Patient Personal Involvement, and communication

The treatment of chronic pain should comply with the following ethical roles. The major ethical issues associated with the design of a study are:

• Patients involved are classifiable by the type of injury and illness. The protocol should consider if they are a vulnerable population (justice).

• The risk net of pain evaluation should consider the efficacy and safety in the protocol design. These risk elements can result in an increase of the pain during the intervention and control (non-maleficence).

• During the clinical trial, the treatment should satisfy the equipoise. The uncertainty of the benefice is one of the main issues, as the treatment should be beneficial. If the benefit is uncertain the treatment is unethical (beneficence).

• Confidentiality is the respect of the sensible data related to patient information. The origin of chronic pain is correlated with personal information such as personal biologic or genetic features or even infection carrying, according to a class of injury or the type of pathology. The participant information must be treated according to the roles expressed in the data protection regulation 2018.

• Voluntarily is part of the patient, ethical respect, so at the beginning of the study, the informed consent must be distributed and signed (autonomy).

In some cases, the incapacity to sign informed consent gives rise to ethical warnings.

DISCUSSION

The public interest can be interested in reducing the burdens afforded by health care to improve the life of patients. The result of a cost-effective analysis is the appraisal of costs. The cost-effectiveness analysis is related to efficacy and safety outcome to reduce the public intervention of patients affected by this disease. Grants can be offered public health system thank this assessment on public and patients' involvement.

This research does a clinical study on new drug combinations against chronic pain. This item needs improvement and a new assessment. Twenty-eight million patients are affected by chronic pain in the United Kingdom. This new combination can decrease the impact on the cost of social health services.

CONCLUSION

The randomised controlled trial is the only type of clinical study that can be used to assess the difference of the outcomes, between the two pharmacological treatments, to improve the condition of chronic pain, the ADRs impact and the related cost-efficacy.

The patients are involved in assessing the improvement of their quality life. They could have ownership of the clinical study thank to the participation in the design. Public interest in cost-effectiveness and related health management helps to retrieve the funding resources.

Double-blind randomised tramadol-controlled trail to appraise the efficacy, the safety and the cost-effectiveness of oral paracetamol and tramadol against oral tramadol only for the treatment of chronic pain.

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