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ENDGAMES

STATISTICAL QUESTION

What are the four phases of clinical research trials?

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Children with neurological and developmental disorders often experience chronic sleep disturbances. Melatonin has been commonly prescribed because of its hypnotic properties. However, trials have had conflicting results. Therefore, researchers assessed the effectiveness of melatonin in treating severe sleep problems in children with neurodevelopmental disorders. A randomised double blind placebo controlled multicentre trial study design was used. The intervention was immediate release melatonin capsules given 45 minutes before the child's bedtime for a period of 12 weeks. Treatment started with a 0.5 mg capsule, and escalated through 2 mg, 6 mg, and 12 mg, depending on the child's response to treatment.[1]

Participants were 146 children who had a severe sleep problem and had not responded to standardised sleep behaviour advice provided to parents four to six weeks before randomisation. Children were recruited from 19 hospitals across England and Wales. The children were randomised to melatonin (n=70) or placebo (n=76).

The outcome measures included subjective (as assessed from sleep diaries completed by the parents) and objective (as recorded by actigraphy) measures of sleep. The researchers reported that children gained little additional sleep on melatonin compared with placebo. However, the children receiving melatonin fell asleep significantly more quickly and they awoke earlier.

Which one of the following best describes the phase of the above clinical trial?

a) Phase I

b) Phase II

c) Phase III

d) Phase IV

Answers

The above trial is best described as a phase III trial (answer *c*).

The development of a drug follows a well established and lengthy process. It may take between 10 and 15 years to develop a new drug from discovery to when it is available for treating patients. Drugs are tested in humans only after they have undergone laboratory testing. Testing in humans is divided into a series of successive clinical trials known as phase I, phase II, phase III, and phase IV trials. These phases are separate clinical studies, and each has a unique objective. Generally, phase I trials establish safety and tolerability in healthy volunteers; phase II trials determine the drugs' efficacy and adverse effects at different dosages in patients; phase III trials establish the effectiveness and safety of the drug compared with placebo or current standard treatment; and phase IV trials determine general risks and benefits after the drug has been licensed. The phases are described in further detail below. As drug development progresses from one phase to the next, the number of participants will typically increase. Drugs that are found to be unsafe or ineffective during development will not progress through all four phases.

Phase I trials are the first stage of drug development in humans. They are conducted on a small number, possibly 20, of healthy volunteers on an inpatient basis. The main aim of a phase I trial is to obtain early indications of the pharmacological actions, safety, and adverse effects of a drug. The drug is typically tested in a single dose to start with. Through the exposure of participants to increasing doses of the drug, a range of safe doses is determined. This allows testing of the pharmacological actions of the drug, and enables researchers to determine how it is processed and tolerated at multiple doses.

Once the initial safety of the drug has been established, the drug will undergo a phase II trial. The purpose of a phase II trial is to investigate the short term safety and therapeutic efficacy of the drug in patients with the disease or condition that the drug is intended to treat. Patients are given the different drug dosages found to be safe in the phase I trial, allowing the drug's efficacy and adverse effects to be compared between different dosages. When the efficacy and safety of the drug have been demonstrated in patients with the disease or condition that the drug is intended to treat, the drug will proceed to a phase III trial.

Phase III trials are the final stage before a new drug is licensed for treating patients. Phase I and II trials tend to be exploratory. By contrast, phase III trials provide confirmation of the properties of the drug discovered in the earlier phases of the drug's development. A randomised placebo controlled trial

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study design will be used. However, if it is unethical to treat patients with a placebo, the current gold standard treatment may be used instead. Phase III trials involve many more participants than previous stages and are often multicentre. The aim is to generate statistically significant data about the safety, efficacy, and dosage of the drug in a large group of patients for whom the drug is intended. Dosages will be modified to determine the one that provides the most beneficial effects with the fewest adverse effects. As in earlier phases, patients are closely monitored for adverse effects, and if serious ones are reported then the trial will be stopped. The phase III trial provides the necessary information for evaluating whether the drug can be approved and licensed. A drug will tend to be licensed only if it shows a worthwhile contribution to medical treatment.

Phase IV trials take place once the drug has been licensed. The drug is evaluated for long periods of time in larger numbers of patients, and possibly subgroups of patients within the population. The aim is to establish the long term efficacy and safety of the drug. The drug may be compared or combined with other available standard treatments. In many respects phase IV trials are similar to phase III trials, although they tend not to be placebo controlled.

The definitions of the four phases of clinical trials are not distinct and there is some overlap between them. Often clinical trials do not fit neatly into one of the four phases described above, and it may not be that simple to discern which phase a trial comes under. The aim of the above trial was to establish the effectiveness of melatonin in treating severe sleep problems in children with neurodevelopmental disorders who had not responded to standardised sleep behaviour advice. Previous trials had had conflicting results. The trial focused on confirming the properties of melatonin that were discovered in earlier trials and therefore it is probably best described as a phase III trial. The trial would not be a phase IV trial because melatonin had not been shown to be effective in treating severe sleep problems in children with neurodevelopmental disorders, and therefore would not be licensed for use as described.

Competing interests: None declared.

1 Gringras P, Gamble C, Jones AP, Wiggs L, Williamson PR, Sutcliffe A, et al; on behalf of the MENDS Study Group. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ* 2012;345:e6664.

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