Opinion regarding the use of placebos in therapeutic antidepressant testing.Report.

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Opinion

Clinical study programmes designed to get the fastest results to prove that a new molecule has a specific psychotropic effect on depressed patients justify placebo-control.

However both the inherent risks or discomfort of depressive pathology and its sensitivity to the placebo effect require special precautions in the choice of criteria for inclusion and in the way therapeutic tests are carried out.

Testing in a hospital setting for development of a substance

- Adult patients who have not given their consent to the principle of the test, or who are not capable of giving truly informed consent, and patients who's state is too serious or for whom the case history requires the immediate use of tried and tested therapy, shall not be included in the study.

- Shall be included in the tests only the minimum number of hospitalised patients necessary for a statistically valid comparison, and only patients suffering from at least an average-intensity depressive syndrome. They will be under close medical supervision in specialised units, experienced in the conduct of biological treatment and in the prevention of suicidal behaviour. The study will be of short duration (of the order of 4 weeks), a sufficient time to judge initial effects of antidepressant activity on mood disorders.

- The experimental test programme should include a provision for premature interruption of the test and replacement of the tested substance by a reference product if evolution of the illness is not such as would be expected of a patient treated with an effective antidepressant (no improvement after a week or 10 days or a fortiori deterioration under treatment).

Long term ambulatory therapeutic tests

- In a later phase, both the negative effects of the long term use of antidepressants or of therapeutic combinations and the risks of recurrence of symptoms under a treatment which is no longer effective are required for global evaluation of the risks incurred by patients under long term treatment.

- Finally, for patients stabilised by initial treatment, continued testing in the long term calls for several recommendations: particularly the quality of specialised medical supervision (means of reaching patients, supervision of adherence to therapy, detection of suicidal risk factors) and the modification of treatment as soon as mood fluctuations judged to be clinically significant are observed.

The National Consultative Ethics Committee accepts this type of therapeutic test under the condition that the above rules are strictly adhered to as they reduce the potential risks to this type of patient as much as possible, while retaining the value of the experimentation. The specific problem here considered for depressed subjects merits a wider reflection extended to the general population to consider the value of placebo testing and the rules to be applied.

Report

Introduction

For depressive syndromes, as for any other pathology, marketing a product without proven therapeutic effectiveness cannot be tolerated. Clinical studies should therefore demonstrate antidepressant activity unambiguously and provide precise information on effective dosage. Clinical study programmes able to get the fastest results to prove that a new substance has a specific psychotropic effect on depressed patients are placebo-controlled.

The use of placebos for depression may raise no strictly specific problem. However, some characteristics of depression syndromes and their treatment call for special recommendations as to the conduct of therapeutic testing. The main specific aspects of depression syndromes are, on the one hand, their sensitivity to the placebo effect, very variable from one group of depressed patients to the next, and on the other, the risk of suicide, much higher for depressed patients or those with mixed symptoms, anxiety and depression, than for patients with pure anxiety symptoms.

Indeed positive response to placebo, which averages 30% for depressed patients, in fact varies from 3-5% among some groups having shown resistance to various (psychological or biological) a priori well applied therapies, to more than 50% among other samples of patients. It should be recalled that the average success rate for antidepressants is no higher than 60 to 70% and that we have no way of knowing in advance which patient will show significant and stable improvement under placebo and which other will benefit from antidepressant chemotherapy despite its inherent drawbacks.

The purpose of this report is to establish the conditions under which placebo-control is ethically acceptable for depressed patients included in therapeutic tests. We will successively consider the practical problems raised by inclusion of these patients in such clinical testing, and subsequently the methods which can be applied to placebo tests.

Bibliography

The main documents used to prepare this text are:

-The document published by FUAG (France-Université, Antidépresseurs: Groupe d'études - French University Study Group, Antidepressants "Placebos in Antidepressant Therapeutic Testing" (1989)

- A document published by the Commission of the European Community to assist applicants for marketing authorisation for new substances in applying the Directives of the EEC: " *The Rules Governing Medicinal Products in the European Community Volume III and its Addendum: Guidelines on the quality, safety and efficacy of medicinal products for human*

use, chapter on : "Clinical Studies of Antidepressant Medication " (The Rules Governing Medicinal Products in the European Community Volume III).

Depression : syndrome or symptom ? Diagnostic criteria. Inclusion in trial

Definitions

A product can be considered an antidepressant only when its efficacy in treatment of manifest depressive syndromes has been demonstrated. These syndromes are differentiated from simple dysphoric symptoms by the duration and seriousness of the mood disorder and by the presence of associated symptoms such as restlessness, lethargy, sleep disorders, feelings of inferiority or guilt. The depressive syndrome itself can be classified and quantified by study of personal and family history, thus for instance distinguishing between primary isolated depression, depression secondary to another illness, endogenous and non-endogenous depression, unipolar or bipolar. The value of such distinctions is that they may soon allow correlation between recent knowledge acquired in genetics and biology and biochemistry in the field of depression, with data from studies of differential therapeutic reactivity in patients.

Criteria for inclusion

Constitution of sufficiently homogeneous subgroups of patients requires that patients to be included in the tests be first classified according to precise and internationally widely used diagnostic criteria. Such can be found at this time in the American document, *Research Diagnostic Criteria* (RDC), and in those of *the Diagnostic and Statistical Manual of Mental Disorders* , now in its third revised edition, DSM III-R, published in 1987.

The diagnostic criteria of the second revision of the *International Classification of Diseases* , ICD-10, Geneva, 1992, can also be used.

Furthermore, the criteria for inclusion must necessarily include an indication of the *extent and seriousness* of the depressive syndrome. Indeed the symptoms of depression must be sufficiently manifest and unmistakable for the efficacy of the treatment to be revealed. A number of evaluation scales or questionnaires on the symptoms of depression are available, which when used jointly make it possible to globally evaluate the seriousness of the depression and each patient's symptomatic profile and their evolution under treatment.

Comparative testing: reference product or placebo ?

To correctly evaluate the efficacy of a presumed antidepressant, from a scientific point of view, it is best, from the start of controlled tests, to use randomised double-blind testing against placebo. Comparison with placebo is also suitable to differentiate morbid manifestations (notably somatic symptoms of depression) from side effects of the substance.

In comparisons of an experimental product and a reference product, the absence of statistically significant differences does not necessarily imply therapeutic equivalence. In so called equivalence tests, it is apparent that several hundred patients are required. In fact it is essential to contemplate such tests only after one or two preliminary studies against placebo have given conclusive results. On this subject, experience shows that 30 to 50 patients per treatment group is enough to make the comparison between a pharmacologically active product and a placebo yield statistically significant differences on the classic scales of depression. However, from an ethical point of view, the use of placebos can be contemplated only if "all precautions have been taken to minimise the impact of the

study and the discomfort it can engender" (Explanatory notes, The Rules Governing Medicinal Products, EEC Volume III).

There are numerous criteria for not including subjects in these trials. Some are general in nature, not specific to depressed patients, such as excluding minors or adults who have not accepted the very principle of comparative testing. Others are specific to certain types of depressed patients. Finally, if inclusion in a trial seems justified, many conditions in the conduct of the testing must be met for the trial to be acceptable from an ethical viewpoint.

The first reason for not including a patient involves the notion of informed consent. Indeed, some depressed patients are not capable of giving valid consent (for example in some serious depressions with intense melancholy and delusions).

The other main depression related reasons not to include patients are as follows:

- symptoms of low intensity for which it is difficult to demonstrate a significant difference of activity with a placebo,

- on the contrary, depressive syndromes serious enough, or with history such that it is necessary from the outset to use tried and tested techniques such as sismotherapy or infusion of antidepressants due to the urgency or even the life threatening nature of the problem (suicide overall bodily harm),

It also seems necessary not to include in such trials patients who have, in the past, shown very good response to a well known and well tolerated antidepressant.

Finally, the main conditions of the therapeutic tests which must imperatively be applied to make the trial acceptable are as follows:

- only the minimum number of patients necessary to obtain statistically valid results should be included;

- only patients with a manifest depressive syndrome of at least medium or moderate intensity are to be included, and they should be under close medical supervision, in a hospital setting, in special units trained in the conduct of biological treatment and in the prevention of suicidal behaviour;

- test should last only long enough to demonstrate initial antidepressant response, i.e. 4 weeks;

- also, the experimental programme must include a provision to prematurely terminate the trial (either the experimental substance or the placebo) and replace it with a reference product, as soon as it is apparent that the evolution is not what is expected for a patient treated with an effective antidepressant, i.e. no initial improvement after a week or ten days, and a fortiori deterioration under treatment.

It is generally considered that two or maybe three weeks are necessary to be able to judge a specific thymoleptic effect. However, with the exception of some cases of depression which first manifest themselves late in life, after 50, the first signs of improvement generally concern non-specific symptoms such as sleep disorders or somatic anxiety symptoms, as early as the first few days of treatment. This precocious effect might even be predictive of the result ultimately observed.

When all these conditions are met, including depressed hospital patients in placebo controlled trials does not constitute a disadvantage or reduction of their chances with regard to the risk of suicide, as has been established in several recent publications. In fact, out of more than 220 trials surveyed (including 60% on ambulatory patients) concerning patients included in therapeutic tests (2168 under placebo and 14763 treated with an experimental substance or a reference product) the following statistics were noted: 0 suicides under

placebo, 0.9% with an experimental product, 1.2% with a reference product. Regarding suicide attempts: 1.8% under placebo, 2.9% with an experimental substance, 2.2% with a reference product. (Ph. Cialdella and J.P. Boissel: Suicide Risk in Clinical Antidepressant Trials: Placebo and Active Molecules. Placebos in therapeutic antidepressant trials, Fuag, Lyon, 1989). In interpreting these results, the quality of supervision of patients included in the therapeutic tests should be taken into account as well as the degree of danger of antidepressants in cases of voluntary absorption of toxic substances.

Careful attention should be paid to the case of potentially suicidal patients. A classic solution is to exclude "high suicidal risk" patients from placebo trials. The precise estimate of risk for a given individual is actually very questionable. Alternative strategies were suggested in the Symposium organised in 1990 by FUAG on "Suicidal Risk and Therapeutic Tests", concerning true prevention of suicidal behaviour in specialised centres. In this regard the following factors should be taken into account: the quality of supervision and a better detection of indisputably aggravating factors such as restless anxiety, previous history of actual suicide attempts, and social isolation. In these cases, patients should not be a priori excluded from a controlled test, but increased hospital supervision and associated treatment with sufficient doses of neuroleptic type sedatives are systematically recommended.

Other conditions of use of placebos in tests

Placebo and pre-testing periods

An initial period of placebo treatment, generally prescribed under single-blind conditions, is often used before undertaking a therapeutic trial. This period is used to identify subjects unusually sensitive to the placebo effect (who should not be included), to eliminate traces of a previous treatment and to establish a sufficiently stable pre-therapeutic baseline. An adequate duration for this pre-testing period is usually considered to be 3 to 7 days. Depending on the nature of the previous treatment, this period may be too short.

Later comparative testing

(phase III of the programme)

When the initial phase has demonstrated the efficacy of the new substance in hospitalised patients, other types of tests can justifiably be considered, such as ambulatory tests, either for mild depression or for recurrent depression in tests with a prophylactic objective. Prophylactic testing to avoid relapse or recurrence of depression raises relatively specific problems. The risk of relapse (re-emergence of symptoms in an ongoing episode) or of recurrence (a new episode) in recurrent depression, is indeed more pronounced for placebo-treated groups than for those treated with effective antidepressants (50% versus 20 to 25% over a period of 12 to 18 months).

For a global evaluation of the risk to patients, it is necessary to jointly consider the drawbacks inherent in the long term use of antidepressants and the problems linked to the risk of recurrence of symptoms when the treatment is no longer effective. For depressed subjects whose condition has been improved and stabilised by initial treatment, two measures would seem to guarantee limited risk: the quality of specialised medical supervision (means for contacting a patient who has not reported for a scheduled checkup, verification of adherence to therapy, detection of suicidal risk factors) and the decision to modify the treatment as soon as mood fluctuations judged to be clinically significant are detected.

Controlled double-blind tests on parallel groups must be carried out to institute prophylactic actions. For bipolar patients the reference products are lithium salts and Tégrétol*. For unipolar recurrent patients "key comparisons should be made with a placebo. Generally, the

duration of such studies must be one year at least, but two years or more are sometimes found to be necessary" (Explanatory notes: *The Rules Governing Medicinal Products - EEC Volume III*). Here again, the quality and regularity of specialised supervision are best able to guarantee minimum risk.