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Oscillococcinum for influenza treatment

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Summary. The use of a complementary medicine approach, and specifically of the popular medicine *Oscillococcinum*, for the treatment of influenza-like syndromes remains controversial. This brief paper analyses the currently available literature on this homeopathic preparation and the Cochrane Collaboration's 2006 systematic review, along with other recent studies, in order to clarify certain fundamental aspects of its use in the treatment of influenza. In the light of the reported findings, and applying the rigorous criteria of evidence-based medicine, we suggest that this medicine should be placed in category "BI".

Key words: Oscillococcinum, efficacy, safety, evidence based medicine, randomized controlled trials.

Riassunto *(*Oscillococcinum *nel trattamento dell'influenza)*. È ad oggi ancora controverso il ruolo e l'approccio della medicina complementare nel trattamento di sindromi simil-influenzali, ed in particolare del noto medicinale omeopatico *Oscillococcinum*. Questa breve nota analizza la letteratura attualmente disponibile per questo medicinale, comprendente studi originali e la revisione sistematica della Cochrane Collaboration 2006, con lo scopo di chiarire alcuni aspetti fondamentali del suo uso. Alla luce delle prove fornite e in base ai rigorosi criteri della medicina basata sulle evidenze, si suggerisce che *Oscillococcinum* sia considerato nella categoria "BI".

Parole chiave: Oscillococcinum, efficacia, sicurezza, medicina basata sull'evidenza, studi controllati randomizzati.

INTRODUCTION

Oscillococcinum is a unique, original and patented homeopathic medicine produced by Laboratoires Boiron. It is prepared as a Korsakovian dilution (200K) of a specific extract of duck liver and heart. For the preparation of Korsakovian dilutions, Laboratoires Boiron use a patented, fully automated machine designed to ensure perfect reproducibility of dilutions. This homeopathic medicine is officially recognised in Italy by AIFA (Italian Pharmaceuticals Agency) and registered in other countries such as France, where it has been authorised since 1944, and is sold in over 80 countries around the world. *Oscillococcinum* is a "homeopathic medicine", in that it conforms to the definition introduced by Directive 92/73/EEC and reiterated in Directive 2001/83/EC, adopted in Italy with Legislative Decree 185/95 and Decree n. 219 of 24 April 2006. It is used for the prevention and treatment of influenza and viruses that cause influenza-like syndromes.

A careful analysis of the individual studies investigating the efficacy of *Oscillococcinum* [1- 3], along with the recommendations of a recent review [4] and an article published online (www.farmacovigilanza.org), suggest that the conclusions of the recent Cochrane Review by Vickers *et al.* (2006) need to be reconsidered in a different light [5]. This paper reports and discusses in detail the currently available scientific literature dealing with *Oscillococcinum*, clarifying certain fundamental aspects of this pharmacological treatment. The conclusion is that the level of evidence and recommendation grade for this homeopathic medicine need to be better defined.

ANALYSIS OF THE LITERATURE

Below we shall analyse in detail the 3 studies considered (the Casanova trials of 1988, 1984 and 1992 have, for the sake of simplicity, been grouped together as a single trial) in the Cochrane Review [5] and in the articles [1-3], the details of which are summarised in *Table 1*.

Casanova and Gerard, 1988 [1]: the randomised double-blind study involved 27 general practitioners distributed across France, who evaluated 300 patients of both sexes (ranging in age from 25 to 65 years) presenting symptoms of influenza such as body temperature ≥ 38 °C, shivering and muscle-skeletal pain. The studied patients received one tube of *Oscillococcinum* or placebo in the morning and one at night for one week of treatment. Body temperature was significantly decreased in the *Oscillococcinum*-treated group (compared to the placebo group) as early as day 2 (evening body temperature in °C: 38.7 ± 0.52 *vs* 39.2 ± 0.96, $p < 0.0001$), with the greatest reduction observed on day 4 (evening body temperature in °C: 37.2 ± 0.42 *vs* 38.1 ± 1.01, $p < 0.0001$). Furthermore, shivering and myalgia were also significantly reduced in patients treated with *Oscillococcinum*. In particu-

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Table 1 | Oscillococcinum *randomized controlled trials*

Authors and year (ref. n.)	Study and publication type	Number of subjects	Conditions (diagnosis)	Treatment (s)	Outcomes	Treatment compliance	Key results
Casanova *et al.* 1988 [1]	a, c	300	Influenza-like syndrome	***Oscillococcinum (Anas barbariae*** 200K) 1 dose in the morning and 1 in the evening for 3-4 days	Temperature, shivering and myalgia	Information not available	In the verum group: faster temperature reduction, significantly less shivering and less myalgia after 4 days
Ferley *et al.* 1989 [2]	a, b	478	Influenza-like syndrome	***Oscillococcinum (Anas barbariae*** 200K) 5 doses, one every 12 h	Healing rate at 48 h after diagnosis based on rectal temperature and two of the following symptoms: headache, stiffness, lumbar pain, articular ache, shivering.	Information not available	Clinical healing after 48 h and rate of temperature reduction better in the verum group.
Papp *et al.* 1998 [3]	a, b	372	Influenza-like syndrome	***Oscillococcinum (Anas barbariae*** 200K) 1 dose for 3 time/day for 3 days	Evaluation of symptoms during time after treatment	95.7% in the verum group and 89.1% in the placebo group	Statistically significant reduction of symptoms after 48 h in the verum group

(a): Double-blind placebo-controlled randomized clinical trial; (b) high-quality paper in medical literature; (c) paper published in non-indexed medical literature.

lar, myalgia disappeared on the 4th day in 70% of patients treated with *Oscillococcinum*, compared to 48% of patients in the control group ($p < 0.0001$). The differences between the two groups were found to be statistically significant, and demonstrate the efficacy of *Oscillococcinum* in reducing the duration of the influenza illness. The main findings of this study show that *Oscillococcinum* is effective in treating influenza syndrome, in that it more rapidly relieves the characteristic symptoms of this illness compared to placebo. The authors recommend that further studies should be based on serological data rather than on symptoms alone. This first investigation was published in a non-indexed complementary journal, but was followed by two other publications of higher quality, which reported similar results.

Ferley *et al.*, 1989 [2]: the randomised, double blind study involved 478 patients of both sexes, over 12 years of age (237 in the *Oscillococcinum* group and 241 in the placebo group) who, at the time of enrolment in the study, presented rectal temperature above 38 °C and at least 2 symptoms such as headache, stiffness, lumbar pain, joint pain and shivering. Seventy-one% of patients were enrolled during the height of the influenza season (as defined by the French Ministry of Health). The patients in the study received one tube of *Oscillococcinum* or placebo in the morning, and one tube every 12 hours for 2 days. The proportion of cases resolved in the first 48 hours of treatment was higher in the *verum* group compared to the placebo group (17.1% *vs* 10.3%, $p = 0.03$). This corresponded to a risk reduction of 1.67 (95% CI 1.1-2.7, $p = 0.03$). The results were better for the subgroup aged 12-29 years (25% *vs* 8.1%, $p < 0.01$), compared to the subgroup aged > 30 years (10.6% *vs* 8.4%, $p = 0.56$), and for the subgroup with slight-moderate syndrome (24.6% *vs* 11.9%, $p < 0.01$), compared to the subgroup with severe syndrome (7.1% *vs* 8.2%, $p = 0.8$). A greater number of patients in the control group resorted to other drugs for the treatment of fever and myalgia during the first 48 hours (50.2% *vs* 40.7%, $p = 0.04$). The number of patients who positively evaluated the treatment was higher in the treatment group (61.2% *vs* 49.3%, $p = 0.02$). Overall, this study showed that patients with influenza-like syndrome who were treated with *Oscillococcinum* showed an improved (*i.e.* earlier) recovery rate than patients receiving placebo. It is interesting that this homeopathic medicine was more effective in patients aged < 30 years, suggesting that the action of *Oscillococcinum* was more active against the influenza virus.

Papp *et al.* 1998. [3]: the randomised, double blind study involved 372 patients (188 treated with *Oscillococcinum* and 187 with placebo) of both sexes, ranging in age from 12 to 60, who at the time of enrolment presented rectal temperature ≥ 38 °C, muscle pains, headache, or at least one of the following symptoms: shivering, chest or periarticular pain, spine pain, coughing, irritation of nasal mucosa, feeling of malaise. Patients received 3 tubes of *Oscillococcinum* or placebo each day (morning, noon and night) for 3 days. In particular, data were collected concerning the patients' condition 48 hours after the onset of the influenza syndrome, the speed of recovery from the symptoms present at the time of enrolment, and the use of concomitant therapies. The intensity of symptoms was considered on average and moderate, and efficacy was defined as a statistically significant abatement of symptoms. The results of the trial show a highly statistically significant difference between the two groups, for what concerns disappearance of symptoms after 48 hours (19.2% in the *Oscillococcinum* group *vs* 17.1% in the placebo group) and improvement in symptoms (43.7% *vs* 38.6% for placebo) (Krauth test, p = 0.0028). Moreover, the frequency of use of concomitant medicines was slightly higher for the placebo group, as was also the use of multiple medicines. Only 13.8% of the *Oscillococcinum* group used two or three drugs (analgesics and antirheumatics), against 19.6% in the placebo group. Another parameter considered was the percentage of patients able to return to work, which was higher in the *Oscillococcinum* group, both 2 days after the onset of the illness (16.3% against 9.3%) and after 4 days, with highly significant differences. After 7 days, these differences decreased until they became no longer statistically significant. This is unsurprising, considering that the illness in any case has a duration of 5-10 days, even without treatment. This clinical trial provides evidence that the treatment of influenza-like syndromes with *Oscillococcinum* is beneficial, in terms of symptom relief and illness duration.

Reviews and meta analysis: the Cochrane Review on *Oscillococcinum* [5] concludes that:

1) *Oscillococcinum* reduced the time needed for recovery by 0.26 days (95% CI 0.47-0.05), relative to an average duration of illness of 4.9 days. This effect could range from half a day to approximately one hour;
2) the number of days needed to return to work was significantly reduced: 0.49 days less (95% CI 0.89-0.08) compared to the control (average of 4.1 days);
3) *Oscillococcinum* increased the likelihood of recovery within 48 hours of starting treatment: from the two studies which report this data, it can be seen that non-recovered patients were slightly fewer in the *verum* group (339/416) than in the placebo group (365/418). The difference is statistically significant and corresponds to a relative risk of 0.93, that is to say that at 48 hours the difference in favour of *Oscillococcinum* is 0.93 compared to 1.0.

The strongest result, according to the Cochrane authors, is the patients' subjective assessment of the treatment. That is to say, whether they considered the treatment to be effective, and whether this judgement differed between the verum and placebo groups. All three studies (for Casanova the 1984 trial is cited, but the substance does not change, as the Cochrane Review itself reports) were in this respect in favour of the homeopathic medicine: the relative risk was 0.60 (0.37-0.98), meaning that the proportion of patients treated with *Oscillococcinum* who considered the treatment to be useless was 0.6, relative to 1.0 for the placebo (difference of 40%).

In addition to the Cochrane Review, other recent studies have also dealt with the historical origins, scientific basis and strength of evidence of complementary therapies for influenza and viral infections of the upper airways [4-11]. The latter review [11] states that *"There are some positive findings suggesting that* Oscillococcinum *may reduce the duration of influenza, but the effect size tends to be small."* What "small" actually means remains a matter of interpretation.

It is also important to note that the indexed homeopathic literature demonstrates an absence of adverse events, given that the first and foremost requirement for any medicine evaluated in clinical and epidemiological trials is safety [6, 10, 12, 13].

DISCUSSION

When assessing medical interventions, there is no general consensus as to the quality criteria for classifying clinical data in terms of treatment outcomes, scientific strength and reliability, and this is particularly true for homeopathic medicines. In practice, there exists a hierarchy of methods, associated with progressively better and hence more rigorous evidence-based medicine for aiding clinical decisions. However, in this analysis we have relied exclusively on the most rigorous "conventional" criteria for evaluation. It is always important to note the manner in which an existing publication has been evaluated [12], and the relevance or importance of the journal in which it appears. Another quality criterion concerns the methods used and described in the paper. This is an indicator used for "weighing" the reliability of results, and especially for "generating" the conclusions. Finally, perhaps the most important criterion is the strength of evidence from randomized controlled trials (RCTs), including the statistical power and difference size.

For what concerns the studies examined by the Cochrane Review [5], the conclusions of the analysis, as also reported in the abstract, are that: *"Though promising, the data were not strong enough to make a general recommendation to use* Oscillococcinum *for first-line treatment of influenza and influenza-like syn-*

dromes. Further research is warranted but the required sample sizes are large". The recommendation in favour or against the use of a treatment (*i.e.* if the data are "strong enough") depends essentially on evaluating its ratio of benefits to risks and the relevance of the considered outcomes. Since *Oscillococcinum* has been on the market for over 80 years without any reported AE, we can assert that this homeopathic medicine has an excellent safety record with no ADRs of class A, B, C, D, E, or F having ever been reported.

Another source of confusion in the Cochrane Review [5], as also in a more recent review dealing with this subject [11], is that the final evaluation and recommendations are based on evidence from different homeopathic medicine, prepared with different source materials (*e.g.* virus vaccines or herbs, which are not contained in *Oscillococcinum*) or by different procedures (*e.g.* Centesimal Hahnemannian procedure *vs* the Korsakovian procedure which is only used for *Oscillococcinum*).

The present work instead only considers and weighs the evidence of randomised trials conducted using the original preparation. A system for grading the level of available scientific data for or against use of a given treatment for a specific medical condition is that established by Natural Standard, an international expert panel founded to provide high-quality, evidence-based information about complementary and alternative therapies (www.naturalstandard.com). Under this system, evidence is classified into 5 grades (Strong, Good, Unclear or conflicting, Fair negative, and Strong negative). A treatment is considered to have a "good scientific foundation" if there is statistically significant evidence of benefit from 1-2 properly randomised trials, backed up by supporting evidence in basic science, animal studies, or theory. The first criterion (statistically significant evidence of benefit) is unquestionably satisfied by *Oscillococcinum*. With respect to the second (theoretical foundation), recent findings suggest that even high homeopathic dilutions may contain some residual trace of the starting material [14], or incorporate structural dishomogeneities in the solvent which may retain some biological and pharmacological activity [15, 16].

Based on the evidence reported in the literature concerning the efficacy of *Oscillococcinum* in the treatment of influenza and influenza-like syndromes, we can assert that this medicine has shown evidence of efficacy in statistical terms, especially given the rigorousness of the studies carried out. According to the rigorous criteria of evidence based medicine (EBM), the homeopathic medicine *Oscillococcinum* has demonstrated, in RCT studies, a statistically significant difference in clinical efficacy compared to placebo, so that its classification as "weak" or "insufficient" or "not strong enough" is highly questionable, and contrasts with the precepts of EBM, which require setting aside subjective bias to consider only objective evaluations drawn from the available clinical evidence.

Currently, antiviral drugs (such as neuraminidase inhibitors) are not indicated in the first line treatment of influenza, because of their adverse effects. The recommended treatment normally consists only of bed rest, supplemented if needed with antipyretics and analgesics. Yet, use of this homeopathic medicine produces a small but significant reduction in the length of the illness, which makes sense for the patient. A further consideration is that, since influenza syndromes affect millions of people, any reduction in the duration of illness and the time taken to resume work will cumulatively have a socially significant effect in absolute terms.

The latest epidemiological views concur that evaluations of clinical trials should give greater weight to subjective aspects, meaning how patients themselves assess their state of health. From the patient's perspective of illness and health, being ill does not so much consist in having an elevated body temperature, as in how the person "experiences" the changes provoked by external aggression, in this case by a virus. In other words, should normalising body temperature be considered more important than the patient reporting that he or she "feels better"? The symptoms have to be considered as an expression of the normal activation of healing mechanisms, so that it might even be unreasonable to attempt to suppress them.

The evaluation of any medical intervention should take into account not just therapeutic efficacy, but also other factors such as adverse events, costs and compliance: in short, an assessment of the ratio of benefits to risks/costs. In this connection, it is necessary to repeat that *Oscillococcinum* has not shown, in all the studies conducted to date, any adverse events.

CONCLUSIONS

Based on the considerations outlined above and the number of clinical studies currently available, we believe *Oscillococcinum* should be assigned to recommendation class I ("generally proven"), since there is evidence derived from multiple controlled randomised clinical trials and/or from systematic reviews of randomised trials. In fact, this classification requires studies with statistically significant evidence of benefit from 1-2 randomised trials, or evidence of benefit from > 1 meta-analysis properly conducted in accordance with the Scottish Intercollegiate Guidelines Network and Natural Standards [17]. Furthermore, given that *Oscillococcinum* complies with the "strength of recommendations" statement that *"There are some doubts as to whether the particular procedure or intervention should always be recommended, but it is believed that its use should be carefully considered"*, this medicine should be raised to category "B".

For each clinical situation and for each patient, the risks must be weighed against the benefits, bearing in mind the qualitative and quantitative effects of using a particular medicine, and the likely progression and outcome of the pathology. Any pharmacological intervention is justified only if the potential benefits are greater than the risks. The decision must be based on

an adequate understanding of the patient, the disease and its natural history, as well as on a knowledge of the treatment and its potential adverse effects, and in this respect *Oscillococcinum* satisfies the requirements of effectiveness and safety.

Conflict of interest statement

The authors work for the Laboratoires Boiron.

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