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Part Two
CLINICAL EXPERIMENTATION WITH EXTRACTS OF ST. JOHN'S WORT IN DEPRESSED PATIENTS – *Results, comparisons and final conclusions of pharmacotherapy against depression*

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INTRODUCTION

The monograph "Hyperici herba (St. John's wort)" of the E Commission gave "*Psychovegetative disorders, depression, states of anxiety and/or nervous restlessness*"(2). as indications for preparations with St. John's wort. According to state-of-the-art scientific knowledge, the alcoholic extracts of St. John's wort, correctly prepared and dosed, are preferably classified as anti-depressants. Psychovegetative disorders, anxiety and/or nervous restlessness can improve – if of depressive origin – with a few weeks of therapy: preparations with St. John's wort, like other anti-depressants, do not have an acute effect and, in this sense, do not act as day sedatives or as somnifacients. Moving away from the indications of the E Commission, since 1998, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), has accepted in requests for new registrations only the indication "*transitory depressive disorders, from mild to moderate grave*" (leaflet) or, respectively "*mild depressive episodes (and of moderate gravity)*" (technical information). This second diagnosis approximately corresponds to the ICD (*Internat. Classification of Diseases)* classification 10:F32.0 and F 32.1 which means that St. John's wort is partially equivalent to synthetic anti-depressants and this also applies to the considerations shown below on the clinical studies of activity and safety.

METHODOLOGY ADOPTED IN CLINICAL EXPERIMENTATION ON ANTI-DEPRESSANTS

Anti-depressant pharmacotherapy, today recognized as valid by experts, began in 1957 with the launch of imipramine. Since then, more than 30 new active ingredients have been added, including, very recently, *the selective serotonin re-uptake inhibitors* (SSRI). On the therapeutic activity of anti-depressants there exist today a total of about 1500 controlled clinical tests (7, 10) the results of which are reciprocally comparable to quite a good extent as the methodology, on which the experiments are based, has not undergone any notable variation for some forty years. Most of the studies use, as a parameter of reference, the Hamilton Depression Scale (HAMD). This objective scale of assessment was published in 1960, a few years after the introduction of the first tricyclic drugs (6). The doctor, taking 17 or 21 characteristic symptoms of depression as a basis, records a number of individual scores which, when summed together, give a total result from which it is possible to make a scale of the gravity of the illness. Values up to 12 come under normality; up to about 20 they can be attributed to mild depression, up to about 25 moderate depression and over 25, serious depression. The success of the therapy can be evaluated by the recession, along the same scale, of the values of the total score obtained.
For about 15 years there have existed binding rules for the clinical tests of anti-depressants, issued both by the FDA and by the European ministerial authorities. A draft dated April 2001, proposed by the *Committee for Proprietary Medical Products* (CPMP) to bring up to date the EU rules, includes the following: patients must be affected by a major depressive pathology (*Major Depressive Disorder*) which is mild, moderate or severe according to the international diagnostic keys DSM VI or ICD 10. In acute depressive episodes (preferably "moderate") the effectiveness must be shown with controlled studies lasting 4-6 weeks; long lasting protective action is checked at a later date. For the medical evaluation of the characteristic symptoms, in addition to the HAMD scale (preferably in the 17 level version) the Montgomery-Asberg-Depression Scale (MADRS) is also recommended. Patients whose total score improves by 50% are considered "*responders*" in both scales (1).

EXPERIMENTATION ON THE ACTIVITY OF THE EXTRACT OF ST. JOHN'S WORT

The traditional therapeutic form in which St. John's wort was used was the tisane, where the single dose corresponded to the aqueous extract of 2-3g of dried drug. If we divide this quantity by the ratios drug: extract of alcoholic extracts used today, the resulting minimum dosage values are equivalent to 300-1000 mg /day of dry extract; the "experimental posology" of the clinical studies described here below are based on these values.
Up to October 2001 the results of 34 controlled studies of therapy using extracts of St. John's wort had been published; these studies included about 3000 patients affected mainly by mild or moderate depression. A selection of experiments from 1990 is shown in Tables 1 and 2. The products under examination contain, as active ingredients, alcoholic extracts prepared with ethanol at 50% or 60% v/v (Tab. 1) or methanolic at 89% (Tab. 2). As comparative therapies, placebos, synthetic anti-depressants or, in one case, baths of light were used.
In the majority of the tests, the criteria of evaluation were the scores or the numbers of responders of the Hamilton Depression Scale (HAMD) or other confirmed psychometric scales.
The tests in the early 1990s, using extracts prepared with ethanol at 50% or 60%, were still performed with liquid preparations and therefore the exact quantity of dry extract administered in these experiments could only be deduced from the data published. Consequently, in the 10 studies selected overall, the doses used vary from 300 to 1050 mg of extract/day. Compared to the placebo, 5 studies showed significant differences in favour of St. John's wort; compared to imipramine or to fluoxetine, the positive results obtained with St. John's wort were equivalent or even better (Table 1). Recently, the provisional data of another study was published, with 207 patients against the placebo; for 6 weeks of therapy, the total score of the MADRS scales decreased from 22 to 14 points whilst that of the extract from 22 to 11.5 ; the difference between the two groups was statistically significant. (5).
Table 1. A selection of 10 clinical controlled studies with preparations of St. John's wort based on ethanolic extracts, in patients affected by depression. For the calculation of the dose in mg., in the case of the liquid preparations, a content of dry residue equal to 10% was hypothesized [Modified from: Schulz, Hänsel and Tyler, 2001 (14)].

First author Year	Number of cases	Dose (mg/day extract)	Length (days)	Therapy of comparison	Responder vs. comparison
gler, 1990	80	4,5 ml (450 mg)	28	Bromazepam	not stated
Harrer, 1991	116	3 ml (300 mg)	42	Placebo	66% vs. 25%
Bergmann, 1993	80	?	42	Amitriptyline	not stated
Quandt, 1993	88	4,5 ml (450 mg)	28	Placebo	71% vs. 7%
Schrader, 1998	159	500 mg	42	Placebo	56% vs. 15%
Laakmann, 1998	147	900 mg	42	Estr. 0,5% hyperforin, placebo	49% vs. 39% vs. 33%
Philipp, 1999	263	1050 mg	56	Imipramine, placebo	76% vs. 67% vs. 63%
Harrer, 1999	149	800 mg	42	Fluoxetine	71% vs. 72%
Schrader, 2000	240	500 mg	42	Fluoxetine	60% vs. 40%
Woelk, 2000	324	500 mg	42	Imipramine	43% vs. 40%

Table 1

For the extract prepared with methanol at 80%, the total results of 12 controlled studies were published after 1990, where 6 were in comparison with a placebo, 2 with imipramine, and one each with maprotiline, amitriptyline, sertraline, therapy with baths of light. The dosage was included between 450 and 1200 mg/day. The statistic analysis of the scores according to the Hamilton scale, showed significant differences between St. John's wort extract and the placebo in 4 of the 6 studies comparing it with a placebo and in the other two a tendency in favour of the former. The 5 studies compared against 4 synthetic anti-depressants showed, in the case of amitriptyline, a significant superiority of the latter after 6 weeks of therapy, whilst the other 4 studies did not show any significant differences in the effectiveness of the treatment (Table 2). Experimentation against the placebo published very recently was performed with 189 patients affected by "Major depression" (DSM VI). After 6 weeks of therapy the total score on the HAMD scale decreased, for the placebo, from 22 to 13 points and, for the extract, from 22 to 10. The "responders" amounted to 43% for the extract and 43% for the placebo, with a statistically significant difference (4).

Table 2. Selection of 11 controlled clinical studies in patients suffering from depression, treated with dry extract prepared with methanol 80% (v/v) [Modified from: Schulz, Hänsel, Tyler, 2001 (14)]

ACTIVITY OF ST. JOHN'S WORT COMPARED TO SYNTHETIC PREPARATIONS.

The overall results of 10 tests carried out with preparations of St. John's wort, against standard synthetic anti-depressants (see tables 1 and 2) show comparable activity.
In treatments with St. John's wort, the personal attitude of comprehension by the doctor which usually emerges in interviews with the patient, takes on particular importance for the success of the therapy which, in the aforementioned tests, is reflected in results that are clearly higher than those of the placebo. This could lead to the claim that the comfortable attitude of the doctor represents the fundamental element of pharmacotherapy with preparations of St. John's wort.
However, a sample of test patients, chosen at random in the documentation prepared for the applications for registration of modern synthetic anti-depressants, contradicts the suspicion that this situation represents a characteristic of the therapy

Table 2

First author Year	Number of cases	Dose (mg/day extract)	Length (days)	Therapy of comparison	Responder vs. comparison
Lehrl, 1993	50	450-900 mg	28	Placebo	42% vs. 25%
Sommer, 1994	105	450-900 mg	28	Placebo	67% vs. 28%
Harrer, 1994	102	900 mg	28	Maprotiline	61% vs. 67%
Hübner, 1994	39	900 mg	28	Placebo	70% vs. 47%
Vorbach, 1994	135	900 mg	42	Imipramine	64% vs. 58%
Hänsgen, 1996	102	900 mg	42	Placebo	70% vs. 24%
Wheatly, 1997	165	900 mg	42	Amitriptyline	60% vs. 78%
Vorbach, 1997	209	800 mg	42	Imipramine	35% vs. 41%
Brenner, 2000	30	900 mg	42	Sertraline	47% vs. 40%
Shelton, 2001	200	900-1200 mg	56	Placebo	33% vs. 21%
Dienel, 2001	189	900 mg	42	Placebo	53% vs. 43%

The results of the studies carried out to date do not show any substantial differences of activity between the two alcoholic extracts and it can be deduced that the threshold of activity against disorders of depressive pathologies could correspond to about 300 mg of extract a day. The preparations of St. John's wort, clinically experimented at the dose of 500-1000 mg of extract a day in patients affected by mild or average depression, were more active than the placebo.

with extracts of St. John's wort. With reference to the *Freedom Information Act*, in force in the United States, the FDA was requested for the documentation relative to the registration of two "selective" anti-depressants, namely NDA 20-031, on the registration of paroxetine and NDA 18-936 on the registration of fluoxetine. The documentation presented to the FDA for the registration of paroxetine in 1992 included 13 tests against a placebo, of which the average score on the HAMD scale after 4 weeks of therapy had decreased to 10.1 for paroxetine and to 6.8 for the placebo. The difference in the calculated therapeutic effect resulted equal to 3.3 points, that is, to less than one-third of the total therapeutic effect (12).
The documentation for the registration of fluoxetine (1988) contained 4 studies against a placebo, one of which was very extensive, with 746 out-patients divided into two more or less equal groups, affected respectively by mild or moderate depression. The study also included three dosages, specifically with 20, 40 and 60 mg/day. The optimum effect was reached with 20 mg/day whilst with 60 mg/day the difference from the placebo was not statistically significant. The reduction in the score of the HAMD scale (Hamilton Total score), after 6 weeks of therapy, was caused by the "psychodynamic" effect of the doctor's attitude for 90% in the patients with mild depression and for 60% in moderate-serious patients and only for 10% and respectively for 40% by the pharmacodynamic action of the medicine (12).
The decisive role of the doctor, for the success of any anti-depressant pharmacotherapy has also been also shown by many other studies, such as a recent test carried out in Norway (NORDEP-I study). To compare the activity of two "modern" anti-depressants, a double blind randomised study was set up in surgery conditions where 61 general practitioners treated 372 depressed patients for a period of 24 weeks. Fig. 1 reproduces the percentages of success of the placebo. The statistical analysis recorded 47% of positive results in the placebo group against 61% in the group treated with sertraline and 54% in the group treated with mianserin (8). The difference of responders between the placebo and sertraline, the better of the two substances, was thus of 14%, a small difference which is to be observed, also because the manufacturer of sertraline is also the sponsor of the study published by Shelton et al. (15) where the difference of responders between the placebo and St. John's wort in patients with mild or moderate-serious depression, was equal to 12%, that is, about the same as the value of the difference between the placebo and sertraline in the NORDEP-I study.
The *Agency for Health Care Policy and Research* in the United States, after a meta-analysis of 80 clinical studies with the most recent anti-depressants, has reached the conclusion that the shares of responders correspond on average to 32% for the placebo and to 50% for the anti-depressant (9, 10). A similar calculation applied to the 21 recent clinical carried out with extracts of St. John's wort and shown in Tables 1 and 2, shows shares of responders of 30% for the placebo (average of 11 studies) and 56% for the drug (average of 19 studies). This means that in anti-depressant pharmacotherapy, independently of the origin of the active ingredients, from one-half to two-thirds of the positive results are to be ascribed to the capacities of self-recovery of the responder patient to the power of stimulation by the doctor and only a smaller part to the pharmacodynamic action of the substances. According to this indication, consequently, the therapist and his/her environment take on greater importance than the drug itself.

ANTI-DEPRESSANTS 1960-2000: A COSTLY MODERNIZATION

Free pharmacotherpay becomes more costly every day and so there is reason to ask in which direction the economic resources for the discovery of new therapies are to be directed and how to optimise their savings. Figure 2 illustrates, in simplified form, the development of anti-depressants in the last fifty years. The activity, measured generally as a percentage of response according to the Hamilton scale, has remained almost constant for the whole period and in 40-70% of cases, as has already been mentioned, independently of the type of drug used. The frequency of the adverse effects, in the past 40 years, has dropped, on the other hand, from 50% of cases, for tricylcic anti-depressants, to the present 20% for SSRI preparations (Selective Serotonin Re-uptake Inhibitors); for St. John's wort preparations, on the other hand, the incidence of adverse effects corresponded, from the very beginning, to about 3% (13).
In order to improve in a relatively modest way the tolerability of synthetic anti-depressants, more than 30 new molecules have had to be put on to the market, subjecting

Results of an out-patients randomised study with two synthetic anti-depressants against a placebo, performed by general practitioners in Norway. It can be noted in this case too how the "favourable attitude of the doctor" represents the determining factor of therapeutic success (from Malt et al., 1999).

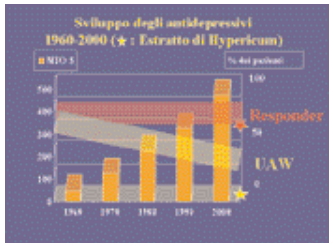
patients to bear the costs of development at a price that has been multiplied by ten, from the initial $50 million to the current $500 million. Extracts of St. John's wort can therefore also avoid such expensive development, without any real therapeutic advantages; whilst showing an effectiveness that is the same or very close to that of synthetic anti-depressants, they are in the position that, as far as the adverse effects are concerned, the synthetic anti-depressants could perhaps reach, extrapolating, in 2030 and, for research costs, those in 1960 (see Figure 2). The improbable differences in effectiveness were perhaps also the reason why the manufacturer of sertraline commissioned a study with extracts of St. John's wort against a placebo, without including its product as the third parameter of experimentation (15).

RULES OF CLINICAL EXPERIMENTATION AGAINST PROFESSIONAL ETHICS

In the context of registration of drugs, the evaluation of effectiveness currently has a preference for the comparison with a placebo to studies of equivalence with standard therapies. Applied to anti-depressants, this procedure may have produced, as a partial consequence, the result that the substances are less active the better they are tolerated (7). Specific adverse effects such as dryness of the throat, visual troubles and dizziness allow the doctor who is an expert in experimentation with synthetic anti-depressants against a placebo to recognize the randomization in 20-50% of patients treated. Generally however, the doctor attributes to the drug, thus identified, greater effectiveness which, due to the few differences between the placebo and the substance in the studies with chemical anti-depressants full of adverse effects, leads to the tendency to favour them statistically to the detriment of St. John's wort preparations which are better tolerated (11).
Errors of evaluation of this type should decrease in the future if, in these experiments, the use of the placebo is prohibited. Anti-depressant pharmacotherapy is recognized as an effective method of treatment. According to article 29 of the Declaration of Helsinki, in the revision of 7th October 2000, the use of a placebo in the context of clinical experimentation is allowed only for the control of those indications for which effective therapeutic methods do not yet exist. Hence, the doctor is forbidden, for ethical reasons, from using any placebo for depressed patients. It is therefore surprising that the draft rules of the CPMP (Committee for Proprietary Medicinal Products) for the clinical tests of anti-depressants, still uses the comparison with a placebo. This motivation also suggests that today, in about two-thirds of all the clinical tests performed, with a third substance, an active control by means of therapy with a registered synthetic anti-depressant, significant differences can no longer be shown with respect to a placebo (1). From certain points of view, this motivation appears worthy of note: it could also lend itself to fuel the well-known doubts of some authors (7) on the pharmacodynamic efficacy of anti-depressants but can in no way justify a violation of the Declaration of Helsinki in its latest version.

SUMMARY

Until the summer of 2001, the results of 34 controlled double blind tests had been published, including about 3000 patients mainly affected by mild or moderate-serious depression. This review has summarized the experiments from 1990 onwards, the results of which, in the majority of cases, were confirmed by the scores or percentages of response which are obtained according to the criteria of the Hamilton Depression Scale (HAMD) .
In 10 of the aforementioned studies, performed with extracts prepared with ethanol at 50% or 60%, the doses varied from 300 to 1050 mg /day. Compared to the placebo, 5 studies showed significant differences of efficacy in favour of St. John's wort; compared to imipramine or fluoxetine, the results were equivalent or even better.
From 1990 onwards, the results of a total of 12 studies were published (6 of which against a placebo, two against imipramine and one each against baths of light, maprotiline, amitriptyline, sertraline) carried out with extract of St. John's wort prepared with methanol at 80%. The dose varied from 450 to 1200 mg of extract/day. The statistical analysis of the total score according to Hamilton showed significant differences in 4 out of the 6 studies against a placebo and, in the other two, a tendency in favour of the extract. In 5 of the studies compared against the 4 synthetic anti-depressants a significant superiority of amitriptyline was observed after 6 weeks of therapy and no significant difference was shown in the other 4 studies.



From 1960 onwards, 30 new synthetic anti-depressants have been introduced all over the world without succeeding in improving their efficacy. The costs of development for each new product are close today to half a billion dollars which, in the end, fall on the welfare insurance bodies although the doctor does not at all feel the need for this updating.
N.B. UAW = Adverse effects

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