Depression Classification of the Patients In Meta-Analyses Studies Affects the

Efficacy of St. John's Wort

by

Heather E. Ovrebo

A PROJECT

submitted to

Oregon State University

University Honors College

in partial fulfillment of
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degree of

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Presented December 3, 1998
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AN ABSTRACT OF THE THESIS OF

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Eight studies from a meta-analysis on St. John's wort by Klaus et. al. (1996)
were analyzed according to the severity of depression manifest by their patients. The
studies were chosen according to inclusion criteria: 1) the study was random, 2) the
study compared St. John's wort to a placebo or an antidepressant, 3) the study was
controlled, 4) the study clearly stated the level of severity of depression demonstrated
by subjects, and 5) the subjects were homogeneous for level of severity. The studies
were then analyzed to determine whether the depression classification had an affect
on the efficacy of St. John's wort. The Mantel-Haenszel test indicated that when the
depression classification is major depression, the odds of improving for the St. John's
wort group is greater than that of the placebo group, and to a lesser extent, the
antidepressant group. The results indicated that the depression classification of the
patients in the studies does affect the efficacy of St. John's wort in the meta-analysis
of Klaus et. al. 1996.

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Depression Classification of The Patients In Meta-Analyses Studies Affects The Efficacy of St. John's Wort

Introduction

Depression is very widespread throughout the U.S. and the rest of the world. It is one of the most common illnesses for which people seek treatment (Vorbach 1994). Antidepressants are the most common form of treatment for depression. However, recently, herbal extracts such as St. John's wort (which is an active ingredient found in the Hypericum plant) are increasing in popularity as a form of treatment for depression. St. John's wort is a member of the Hypericaceae family and has been used for a long time for the treatment of many different illnesses, including depression (Klaus et. al. 1996).

Many studies have been done on the effectiveness of St. John's wort compared to a placebo and compared to antidepressants. One way of comparing these studies is to do a meta-analysis. The essential character of a meta-analysis, according to Smith and Glass, 1981, is that it is the statistical analysis of the summary findings of many empirical studies. A meta-analysis of St. John's wort studies was done by Klaus et. al., 1996. In this meta-analysis, the researchers carefully selected studies which met specific criteria for scientific adequacy. These criteria included that the subjects were randomly assigned to groups, studies that included a control group given no treatment, studies with patients that were depressed, studies that compared St. John's wort to a placebo or an antidepressant or both, and studies that used a clinical outcome measure such as a depression scale in order to assess the drug effects (Klaus et. al. 1996). The meta-analysis included twenty-three randomized clinical studies. Fifteen of these studies compared St. John's wort to a placebo, while eight compared St.

John's wort to an antidepressant. After performing statistical analysis, the conclusion showed that St. John's wort performs better than a placebo in treating depression. However, St. John's wort was not shown to perform any better than current antidepressants in treating depression (Klaus et. al. 1996).

Two other important meta-analyses in psychotherapy research were performed by Smith and Glass, 1977 and Landman and Dawes, 1982. Smith and Glass took 375 evaluations of psychotherapy and counseling and did a meta-analysis on them to determine the effectiveness of psychotherapy. Their main selection criterion was that the study compared a treatment group to an untreated group or a group treated by a different type of therapy (Smith and Glass 1977). The results showed that counseling and psychotherapy do have beneficial effects (Smith and Glass 1977).

Landman and Dawes actually reanalyzed Smith and Glass' 1977 study to look at the quality of the studies used by Smith and Glass. Landman and Dawes examined the procedures used by Smith and Glass to obtain their results. Specifically, Landman and Dawes came up with five issues that they felt needed to be examined to clarify Smith and Glass' conclusions: 1) the fact that there were multiple measures taken from the same subjects, 2) there were measures taken at multiple points in time from the same subjects, 3) there was a nonindependence of scores within a single outcome measure, 4) there was a nonindependence of studies within a single article, and 5) there were nonindependent samples across articles (Landman and Dawes, 1982). Landman and Dawes randomly selected sixty-five studies to reanalyze according to Smith and Glass' meta-analytic techniques. The 65 studies were selected on the basis that they were either compared to a no-treatment group or a placebo group. The

results turned out better than the original conclusions drawn by Smith and Glass that psychotherapy has beneficial effects (Landman and Dawes 1982).

In the meta-analysis of St. John's wort studies by Klaus et. al., 1996, one aspect that was not closely examined was the depression classification of the patients in the studies and how these affected the performance of St. John's wort. The goal of this study was to carefully consider depression classifications of patients in the studies and how these classifications affect the efficacy of St. John's wort.

Method

Procedure

I obtained eight studies used in the meta-analysis of Klaus et. al., 1996 that had a clear depression classification, either mild, moderate, major, or neurotic depressive disorder. The studies all showed that subjects were assigned to control or treatment groups randomly as determined by Klaus et. al., 1996. The depression classifications were obtained from the original studies used by Klaus et. al., 1996. Depression classifications were clearly stated in the studies and were determined, in the case of these studies, by the Hamilton depression scale. The Hamilton depression scale is an observer rated scale that deals mainly with somatic symptoms (Klaus et. al. 1996).

The criteria for inclusion were: 1) the study must be random, 2) the study must compare St. John's wort to a placebo or an antidepressant, 3) the study must have a control group that is given no treatment, 4) the study must clearly state the depression classification of the patients according to a clinical scale, and 5) the

subjects must fall into only one depression classification. Eight studies met these criteria. Six of these studies compared St. John's wort to a placebo and two compared St. John's wort to an antidepressant. Of the studies comparing St. John's wort to a placebo, two were classified as having mildly depressive patients, one had patietns diagnosed with major depression, and three had patients with neurotic depressive disorder. Of the studies comparing St. John's wort to an antidepressant, one was classified as having moderately depressive patients and one was classified as having majorly depressive patients.

Once the depression classification was determined, the improvement of the patients was examined. The patient's improvement was found by looking at Figure 2 of the meta-analysis of Klaus et. al. 1996 p. 256.

Table 1 - Placebo controlled trials of single preparations

	Number of responders	
Study	Hypericum	Control
Haensgen 1994	27/34	9/38
Huebner 1994	14/20	9/20
Lehrl 1993	4/25	2/25
Schmidt 1993	20/32	6/33
Sommer 1994	28/50	13/55
Reh 1992	20/25	11/25

Trials comparing single preparations of St. John's wort and an antidepressant

Harrer 1994	27/51	28/51
Vorbach 1994	42/67	37/68

Statistical Evaluation

The studies were placed in a 2x2 table. The studies comparing St. John's wort to a placebo were analyzed separately from those comparing St. John's wort to an antidepressant.

Table 2 – St. John's wort v. Placebo

Depression Classification	Study	Treatment	Improvement	
			Yes	No
Mild	Huebner 1994	St. John's	14/20	6/20
		Placebo	9/20	11/20
	Sommer 1994	St. John's	28/50	22/50
		Placebo	13/55	42/55
Major	Haensgen 1994	St. John's	27/34	7/34
		Placebo	9/38	29/38
Neurotic	Lehrl 1993	St. John's	4/25	21/25
		Placebo	2/25	23/25
	Schmidt 1993	St. John's	20/32	12/32
		Placebo	6/33	27/33
	Reh 1992	St. John's	20/25	5/25
		Placebo	11/25	14/25

St. John's wort vs. Antidepressant

Depression Classification	Study	Treatment	Improvement

			Yes	No
Moderate	Harrer 1994	St. John's	27/51	24/51
		Maprotiline	28/51	23/51
Major	Vorbach 1994	St. John's	42/67	25/67
		Imipramine	37/68	31/68

The Mantel-Haenszel Test for equal odds in several 2x2 tables was used. Odds ratios were calculated on the basis of whether the patients improved or not and which depression classification they fell into.

Results

The odds ratios for improvement of the patients were highest for the patients classified as having major depression.

Table 3 – St John's wort vs. Placebo

Depression Classification	Odds Ratio
Mild	3.61
Major	12.43
Neurotic	3.9

St. John's wort vs. Antidepressant

Depression Classification	Odds Ratio
Moderate	.9241
Major	1.41

The odds ratios for the studies comparing St. John's wort to a placebo show that when the depression classification for the patients is mild depression, the odds of improving for the St. John's wort group are estimated to be 3.61 times the odds of improvement for the placebo group. When the depression classification is major, the odds of improvement for the St. John's wort group are estimated to be 12.43 times the odds of improvement for the placebo group. Finally, when the depression classification is that of neurotic depressive disorder, the results are pretty much the same as they are for that of mild depression. The odds of improvement for the St. John's wort group are approximately 3.9 times the odds of improvement for the placebo group.

The results of the studies comparing St. John's wort to an antidepressant are not as impressive. When the depression classification is moderate depression, the odds of improvement for the St. John's wort group are about .9241 times the odds of improvement for the antidepressant group. When the depression classification is that of major depression, the odds of improvement for the St. John's wort group are estimated to be 1.41 times the odds of improvement for the antidepressant group.

Discussion

The results indicate that the odds of improving when given St. John's wort is better when the classification of depression is major depression. The results also show that the odds of improving when given St. John's wort is better when it is compared to a placebo and the depression classification is major depression than when it is compared to an antidepressant and the depression classification is major.

The results seem to support the idea that the depression classification of the patients in the meta-analysis of Klaus et. al., 1996 does affect the efficacy of St. John's wort. The odds of improving when given St. John's wort is different when considering the depression classification of the patients in the studies and the treatment that St. John's wort is compared with.

There are a few ways that this study could be improved. One way of improving this study has to do with the number of studies involved. There were so few studies that actually narrowed down the depression classification to one specific category. Most of the studies included patients that fell into more than one depression classification such as mild to moderate, moderate to severe, and other such classifications. It would be ideal to use many other studies that have included patients based on only one clearly defined depression classification.

Another way of improving this study is to consider not just whether St. John's wort performed better than a treatment, but to take into account how much better it actually performed. One of the main strengths of a meta-analysis according to Landman and Dawes, 1982, is that a meta-analysis can "indicate not only whether a treatment makes a difference but also how much of a difference" (Landman and Dawes 505). The way to examine this difference is by statistically coming up with an effect size, which measures the magnitude of the treatment's effect (Landman and Dawes 505). The meta-analysis of Klaus et. al., 1996 did come up with overall effect sizes for the improvement brought about by St. John's wort. In order to enhance this study, these effect sizes could be analyzed to determine if the improvement qualities

of St. John's wort are very considerable when actual effect sizes are taken into account.

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