

# Does St John's Wort improve symptoms of depression?

## Treatment in brief

Extracts of the plant St. John's Wort, have been used in folk medicine for a long time for a range of problems, including depression, anxiety and sleep problems.

## The condition

Depression is common, serious and treatable. Untreated, it can result in disability and even death. It affects 1 in 25 people in any 1 month. It tends to be episodic and of varying severity. Symptoms develop over days to weeks, though there may be symptoms over the preceding months. Half respond to 6–8 weeks of active treatment. The likelihood of recovery decreases with the duration of symptoms. Some people with depression experience continuing symptoms and social and work problems. The more episodes of depression a person experiences, the more likely they are to experience a recurrence.

For the treatment of depression, a variety of antidepressant medications are available that have proven beneficial effects. Other treatments including cognitive behavioural therapy and interpersonal psychotherapy are also used. Treatment varies with type and severity of depressive symptoms. (RANZCP 2004)

## Background

Extracts of the plant *Hypericum perforatum* L. (popularly called St. John's Wort), have been used in folk medicine for a long time for a range of indications, including depressive disorders. Extracts of St. John's Wort are licensed and widely used in Germany for the treatment of anxiety, depressive and sleep disorders. In recent years, St John's Wort has also become very popular in other countries. St John's Wort contains many substances that may contribute to its effects. The exact mechanism of action is still unclear. (Linde, Mulrow et al. 2005)

Depression is a condition that involves a significant and persistent lowering of mood associated with great sadness, and a loss of interest in life. Many people feel sad, discouraged, or "down" once in a while, but for some people, this mood does not go away. When these problems last two weeks or more, and are so bad that they get in the way of daily living, this is depression.

[http://www.infrapsych.com/root/1033/Depression/Depression\\_Symptoms.htm](http://www.infrapsych.com/root/1033/Depression/Depression_Symptoms.htm)

Other symptoms include loss of interest and ability to experience pleasure, irritable rather than depressed or apathetic mood. The following physical symptoms may also be present: changes in appetite and weight, changes in sleep, and fatigue or loss of energy. Thinking may be affected with an increase in guilty and pessimistic thoughts, hopelessness and helplessness, Concentration may be affected and the person may become quite forgetful. Thoughts of death and suicide may be present. (RANZCP 2004)

## The evidence

There is good evidence that St John's Wort improves symptoms of mild to moderate depression. These people may not meet the criteria for major depression. The beneficial effects of St John's Wort have been demonstrated in a systematic review of studies comparing this treatment to placebo and standard

antidepressant treatment. Another two RCTs confirmed that St John's Wort was more effective than placebo and one confirmed that St John's Wort was as effective as a standard antidepressant. This finding was not supported by another RCT but this can be perhaps explained by the study being under-powered.

For major depression the evidence is inconclusive. The systematic review found a small benefit compared to placebo. One RCT found that St John's Wort was as effective as a standard antidepressant. Another supported this finding but could not demonstrate a benefit for St John's Wort or the standard antidepressant over placebo. This could be explained by poor methodological quality and a drop out rate of 47%.

There is good evidence that St John's Wort extracts caused fewer side-effects than older antidepressant but a similar number to selective serotonin reuptake inhibitors.

### **Other important issues**

Many patients buy St John's Wort products from health-food stores and might not disclose this to their doctors. This can be problematic, because serious interactions can occur with a number of frequently used drugs <http://www.medsafe.govt.nz/Profs/PUarticles/sjw.htm>

The quality of Hypericum preparations can also differ considerably, and a number of products contain only minor amounts of bioactive constituents.

More studies that compare specific extracts with both placebo and standard antidepressants in clearly defined patient populations with and without major depression are needed.

## Key messages

There is level 1 evidence that St John's Wort <b>is effective</b> for <b>mild or moderate</b> depression.	1
There is level 4 evidence that St John's Wort <b>may be effective</b> for <b>major</b> depression.	4
There is level 2 evidence that St John's Wort extracts caused fewer side-effects than older antidepressant but a similar number to selective serotonin reuptake inhibitors.	2
There is <b>no evidence</b> about effectiveness in <b>severe</b> depression.	No study evidence
St John's Wort extracts <b>can have serious interactions</b> with a variety of other drugs	
People taking or considering taking St John's Wort <b>should inform</b> their health care practitioner	

1	2	3	4
Evidence with a high degree of reliability	Evidence with reliability, but open to debate	Some evidence without a high degree of reliability	Some evidence, but based on studies without comparable groups.

## The information in this summary was developed by assessing:

Bjerkenstedt, L., G. V. Edman, et al. (2005). "Hypericum extract LI 160 and fluoxetine in mild to moderate depression: A randomized, placebo-controlled multi-center study in outpatients. [References]. European Archives of Psychiatry and Clinical Neuroscience 255(1): 40-47.

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Randlov, C., J. Mehlsen, et al. (2006). "The efficacy of St. John's Wort in patients with minor depressive symptoms or dysthymia--a double-blind placebo-controlled study." Phytomedicine **13**(4): 215-21.

RANZCP (2004). "Australian and New Zealand clinical practice guidelines for the treatment of depression." Australian and New Zealand Journal of Psychiatry **38**(6): 389-407.

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Trautmann-Sponsel, R. D. and A. Dienel (2004). "Safety of Hypericum extract in mildly to moderately depressed outpatients: a review based on data from three randomized, placebo-controlled trials. [Review] [21 refs]." Journal of Affective Disorders **82**(2): 303-7.

Uebelhack, R., J. Gruenwald, et al. (2004). "Efficacy and tolerability of Hypericum extract STW 3-VI in patients with moderate depression: a double-blind, randomized, placebo-controlled clinical trial." Advances in Therapy **21**(4): 265-75.

Werneke, U., O. Horn, et al. (2004). "How effective is St John's wort? The evidence revisited." Journal of Clinical Psychiatry **65**(5): 611-7.

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# Does St John's Wort improve symptoms of depression?

## 1. Abstract

Depression is a common mental illness that involves a significant and persistent lowering of mood associated with great sadness, and a loss of interest in life. When these problems last two weeks or more, and are so bad that they get in the way of daily living, this is depression. Other symptoms include loss of ability to experience pleasure, anxiety, panic, fearfulness, irritability or apathetic mood, changes in appetite and weight, changes in sleep, fatigue or loss of energy, guilty and pessimistic thoughts, hopelessness and helplessness, Concentration may be affected and thoughts of death and suicide may be present.

Depression is common, serious and treatable. Untreated, it can result in disability and even death. It affects 1 in 25 people in any 1 month. Some 43% of those with depression suffer severe disability. It tends to be episodic and of varying severity. Most major depression begins in the late 20s. Symptoms develop over days to weeks, though there may be symptoms over the preceding months. Half respond to 6–8 weeks of active treatment. The likelihood of recovery decreases with the duration of symptoms. Remission is partial for 20–30% of people with depression, who experience continuing symptoms and social and occupational impairment. The more episodes of depression a person experiences, the more likely they are to experience a recurrence.

For the treatment of depression, a variety of antidepressant medications are available that have proven beneficial effects. Other treatments including cognitive behavioural therapy and interpersonal psychotherapy are also used. Treatment varies with type and severity of depressive symptoms.

Extracts of the plant St. John's Wort, have been used in folk medicine for a long time for a range of indications, including depressive disorders, anxiety and sleep disorders. St John's Wort contains at least seven constituents or groups of components that may contribute to its effects. The exact mechanism of action is still unclear.

There is good evidence that St John's Wort improves symptoms of mild to moderate depression. For major depression the evidence is inconclusive.

There is good evidence that St John's Wort extracts caused fewer side-effects than older antidepressant but a similar number to selective serotonin reuptake inhibitors.

Many patients buy St John's Wort products from health-food stores and might not disclose this to their doctors. This can be problematic, because serious interactions can occur with a number of frequently used drugs

## **2. Type of treatment** Herbal

**Scientific name (genus and species):** *Hypericum perforatum*

**Synonyms and common names:** St. John's Wort

**Indication:** Depression, anxiety and sleep disorders

## **3. Background**

Depression is a mood state that involves a significant and persistent lowering of mood associated with great sadness, and a loss of interest in life. Many people feel sad, discouraged, or "down" once in a while, but for some people, this mood does not go away. When these problems last two weeks or more, and are so bad that they get in the way of daily living, this is depression.

[http://www.infrapsych.com/root/1033/Depression/Depression\\_Symptoms.htm](http://www.infrapsych.com/root/1033/Depression/Depression_Symptoms.htm)

Other symptoms include loss of interest and ability to experience pleasure, irritable rather than depressed or apathetic mood. The following physical symptoms may also be present: changes in appetite and weight, changes in sleep, and fatigue or loss of energy. Thinking may be affected with an increase in guilty and pessimistic thoughts, hopelessness and helplessness, Concentration may be affected and the person may become quite forgetful. Thoughts of death and suicide may be present.

Depression is common, serious and treatable. In the Australian Mental Health Survey, 4% of adults had a depressive disorder in the past month. Untreated, it can result in significant disability and even death. Some 43% of those with depression suffer severe disability. It tends to be episodic and of varying severity. Moderate to severe depression is as disabling as heart failure, and its relapsing nature accounts for one of the highest levels of disease burden of any condition. Depression is the most likely condition to co-exist with other physical and psychiatric disorders, and is often unrecognized by healthcare workers.

Depression does occur in children but more often in teenagers. Most major depression begins in the late 20s. Symptoms develop over days to weeks, though there may be anxiety, panic, fearfulness and lowered mood over preceding months. Sudden onset is usually associated with major stress. Untreated moderate episodes last up to 9 months. Half respond to 6–8 weeks of active treatment. The likelihood of recovery decreases with the duration of symptoms. Remission is partial for 20–30% of people with depression, who experience continuing symptoms and social and occupational impairment. The more episodes of depression a person experiences, the more likely they are to experience a recurrence.

If untreated, depression increases risk of suicide and other violent acts. Unemployment, isolation, impulsivity and misuse of alcohol and drugs increase the risk. Depression, especially when recurrent or chronic, distresses family and friends and it may affect a person's capacity to parent, and is often associated with occupational problems.

Many factors protect against, predispose to, or precipitate depression: genes, childhood experience, previous trauma, social and cultural supports, physical factors (including drugs) and stress. Depression occurs more commonly in the young and in women, at least in

Western society. Depression affects about 5–14% of those with medical illness. Rates of 50% are associated with some conditions, for example HIV-AIDS. It is commonly associated with Parkinson's disease, migraine and chronic pain. Increased rates may be a direct effect of physical illness, a side-effect of treatment or a reaction to illness. (RANZCP 2004)

For the treatment of depression, a variety of antidepressant medications are available that have proven beneficial effects. Other treatments including cognitive behavioural therapy and interpersonal psychotherapy are also used. Treatment varies with type and severity of depressive symptoms. (RANZCP 2004) All antidepressant medications have adverse effects, and some are expensive. Additional treatments with little risk, credible benefit, and moderate costs could be a useful addition to depression management.

Extracts of the plant *Hypericum perforatum* L. (popularly called St. John's Wort), have been used in folk medicine for a long time for a range of indications, including depressive disorders. Extracts of St. John's Wort are licensed and widely used in Germany for the treatment of anxiety, depressive and sleep disorders. In recent years, St John's Wort has also become very popular in other countries. St John's Wort contain at least seven constituents or groups of components that may contribute to its pharmacological effects While some isolated substances, as for example hyperforin, have been shown to have antidepressant activity, the total extract seems to be clearly more effective. The exact mechanism of action is still unclear. (Linde, Mulrow et al. 2005)

#### **4. Objectives**

To investigate whether extracts of hypericum are more effective than placebo and as effective as standard antidepressants in the treatment of depressive disorders in adults; and whether they have less adverse effects than standard antidepressant drugs.

#### **5. Criteria for including studies**

*Types of study:* Published systematic reviews or double-blind randomised controlled trials of extracts of St John's Wort versus standard antidepressant treatment or placebo applied for at least 4 weeks; limited to the English language.

*Types of participants:* Adults ( $\geq 18$  years) with a depressive disorder.

*Types of intervention:* Extracts of St John's Wort versus standard antidepressant treatment or placebo.

*Types of outcome measure:* All clinical outcome measures such as depression scales or symptoms.

*Exclusions:* Combined herbal treatments; treatment period of less than 4 weeks; studies examining prevention of depression.

#### **6. Search strategy**

We searched the following databases in May 2006: AMED, The Cochrane Library, PSYCHINFO, MEDLINE, and CINAHL from 2004. We also checked the reference lists of publications retrieved by the search for further relevant studies. We also searched the World Wide Web for any other relevant studies.

## 7. Data Collection, Analysis and Development of Recommendations

We used the above search strategy to obtain titles and abstracts of studies that were potentially relevant to this review. Where studies met the criteria for inclusion, they were assessed in full text. The quality of each study was evaluated using the GATE criteria (<http://www.health.auckland.ac.nz/population-health/epidemiology-biostats/epiq/>) for the evaluation of RCTs and systematic reviews. Where primary studies were included in a good quality systematic review, the systematic review was included rather than the individual primary studies. Where the systematic reviews included the same primary studies, the Cochrane review was used.

The overall quality of the body of evidence (including all the included studies) was graded according to the NZGG CAM levels of evidence system.

Relevant data were extracted from the studies selected for inclusion.

## 8. Description of studies

A Cochrane systematic review, updated in February 2005, was identified. In addition, three other systematic reviews and six additional randomised controlled trials (not included in the systematic reviews) met the criteria for inclusion. The Cochrane review included 37 RCTs, published prior to April 2004. Another systematic review (Werneke, Horn et al. 2004) included 18 RCTs, published prior to September 2003. All these studies were included in the Cochrane systematic review. A systematic review (Knuppel, Geddes et al. 2004) that looked at safety and adverse effects was included. A review (Trautmann-Sponsel and Dienel 2004) of three RCTs was excluded as the studies were included in the Cochrane review. One other RCT (Murck, Fava et al. 2005) was a re-analysis of an RCT already included (Fava, Alpert et al. 2005). The six additional RCTs were all published between July 2004 and 2006.

Summary details of the included studies are as follows:

### *Systematic Reviews*

Study	Participants	Intervention & Comparison	Outcomes measured	Comment
Linde K, 2005  Cochrane Database of Systematic reviews	Included studies: 37 studies published prior to April 2004  N=4925  Adults with depressive disorders	St John's Wort for at least 4 weeks  vs  placebo  standard antidepressants	Assessment of symptoms with a depression scale or general assessment of clinical response	The methodological quality of most of the included studies was reasonable to good.  26 studies used placebo as the comparator; 14 used standard antidepressants
Knuppel, L. 2004  Germany	Included studies: 35 RCTs and 17 observational studies	St John's Wort for at least 4 weeks  vs  placebo  standard antidepressants	Drop outs due to adverse effects  Numbers reporting adverse effects	Drop out rates and adverse effects are similar for St John's Wort, SSRIs and no treatment  St John's Wort is better tolerated than older standard antidepressants  Short follow up periods and small sample sizes may increase the chance that adverse effects are overlooked

Werneke, U. 2004 UK	Included studies: 18 studies	St John's Wort  vs  placebo	Hamilton depression scale	All studies were included in the above Cochrane review so this systematic review was not used
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### *Randomised controlled trials*

Study	Participants	Intervention & Comparison	Outcomes measured	Comment
Gastpar, M 2005 Multicentre trial in Germany	241 patients with moderate depression	Hypericum extract 612mg once daily  vs  sertraline 50mg once daily  Duration 12 weeks  Follow-up 24 weeks	Hamilton depression scale  Von Zerssen's Adjective Mood Scale  Clinical Global Impression  Adverse events	Blinded  Drop out 17% at 12 weeks
Randlov, C. 2006 Denmark	150 patients with mild or moderate depressive episode or dysthymia  Mean age 50.9 years (range 23-74)  113 women; 37 men	Hypericum extract either 0.12% hypericine (low-dose) or 0.18% hypericine (high-dose) taken 3 times daily  vs  placebo  Duration 6 weeks	Hamilton depression scale  Beck depression inventory  Visual analogue scale  D-2-test  Adverse events	Blinded  Drop out rate 14%  Ad hoc statistical analysis  No power calculation
Szegedi, A. 2005 Germany	251 adult outpatients with acute major depression	Hypericum extract (WS 5570) 300mg three times a day  vs  Paroxetine 20mg once daily  Duration 6 weeks	Hamilton depression scale  Montgomery-Åsberg depression rating scale  Beck depression inventory  Clinical Global Impression  Adverse events	Mean age and average duration of current episode were higher in the St John's Wort group  Blinded  Power calculation  Drop out rate 18%
Bjerkstedt, L 2005 Sweden	163 adults from 15 GP practises with mild to moderate major depression	Hypericum extract (LI160) 300mg three times a day  vs  Fluoxetine 20mg daily  vs  Placebo  Duration 6 weeks	Hamilton depression scale  Montgomery-Åsberg depression rating scale  Clinical Global Impression  Adverse events	Blinded  Drop out rate from ITT population 9%  Drop-outs after start of treatment but before first follow-up were excluded from ITT analysis  No placebo group at week 6 since the placebo group was switched to either active treatment groups after 4 weeks

Fava, M 2005 Germany	135 adult outpatients with major depression  Mean age 37.3	Hypericum extract (LI160) 300mg three times a day  Vs Fluoxetine 20mg daily  Vs Placebo  Duration 12 weeks	Hamilton depression scale  Beck depression inventory  Clinical Global Impression  Adverse events	Blinding  Drop out rate 47%  ITT analysis
Uebelhack, R. 2004 Germany	140 outpatients with moderate depressive disorder  46 men; 94 women	Hypericum extract (STW 3-VI) 900mg once daily  vs Placebo  Duration 6 weeks	Hamilton depression scale  Von Zerssen's Adjective Mood Scale  Clinical Global Impression  Adverse events	Blinding  Drop out rate 14%  ITT analysis

## 9. Methodological quality

The included studies were evaluated using the GATE criteria. The two systematic reviews were of good quality. Most of the included studies had fair to good methodological quality. Three RCTs were of good quality, two of fair quality, and one poor.

## 10. Results

The Cochrane review:

In this meta-analysis, St John's Wort extracts were found to improve symptoms more than placebo and similarly to standard antidepressants in adults with mild to moderate depression. However, when looking at only major depression, the systematic review shows a very small benefit of St John's Wort compared to placebo.

St John's Wort extracts caused fewer side-effects than older antidepressant but a similar number to selective serotonin reuptake inhibitors (SSRIs).

Placebo comparisons – there were 26 studies involving 3320 participants. Older studies differed from more recent ones in several respects: older studies were in German-language countries, had smaller sample sizes, were of shorter duration, and their methodological quality tended to be lower. The newer studies more often were restricted to patients with major depression and the patients tended to have more severe depression.

In those studies restricted to major depression, the smaller (less precise) studies found a response rate of 2.06 (95% CI 1.65-2.59) and the larger (more precise) studies found a response rate of 1.15 (95% CI 1.02-1.29).

In those studies not restricted to major depression, the smaller (less precise) studies found a response rate of 6.13 (95% CI 3.63-10.38) and the larger (more precise) studies found a response rate of 1.17 (95% CI 1.40-2.09).

Standard antidepressant comparisons – there were 14 studies involving 2283 participants. All studies but one included only participants with major depression. Response rates were similar for St John’s Wort compared to standard antidepressants (RR 1.01, 95% CI 0.93-1.10).

Safety – Compared to placebo, there was a similar drop-out rate for any reason (OR 0.83, 95% CI 0.64-1.06), drop-outs due to adverse effects (OR 0.60, 95% CI 0.28-1.30) and reporting of adverse effects (OR 0.79, 95% CI 0.61-1.03)

Compared to standard antidepressants, participants taking St John’s Wort were less likely to drop out (OR 0.65, 95% CI 0.46-0.92), to drop out due to adverse effects (OR 0.25, 95% CI 0.14-0.45), and to report adverse effects (OR 0.39, 95% CI 0.31-0.50). Compared to SSRIs], the probability to drop out was similar in those taking St John’s Wort.

*St John’s Wort vs placebo*

Comparison		Study size	Response rate	95% Confidence interval
Placebo	Major depression only	Smaller	2.06	1.65-2.59
		Larger	1.15	1.02-1.29
	Not restricted to major depression	Smaller	6.13	3.63-10.38
		Larger	1.17	1.40-2.09

*St John’s Wort vs standard antidepressant*

Type of antidepressant	Response rate	95% Confidence interval
All types	1.01	0.93-1.10
Older antidepressants	1.03	0.93-1.14
SSRIs	0.98	0.85-1.12

*Safety*

Comparison		Odds ratio	95% Confidence interval
Placebo	Drop out for any reason	0.83	0.64-1.06
	Drop out due to adverse effect	0.60	0.28-1.30
	Reporting of adverse effect	0.79	0.61-1.03
Antidepressants	Drop out for any reason	0.65	0.46-0.92
	Drop out due to adverse	0.25	0.14-0.45

	effect		
	Reporting of adverse effect	0.39	0.31-0.50
Older antidepressants	Drop out due to adverse effect	0.25	0.14-0.45
SSRIs	Drop out due to adverse effect	0.06	0.31-1.15

The other systematic review (Knuppel, Geddes et al. 2004) looked at safety and adverse events. Information from 35 double-blind randomized trials showed that dropout and adverse effects rates in patients receiving hypericum extracts were similar to placebo, lower than with older antidepressants, and slightly lower than with selective serotonin reuptake inhibitors. Dropout rates due to adverse effects in 17 observational studies including 35,562 patients ranged from 0% to 5.7%. Serious interactions or adverse effects were not reported in any study. Published cases and cases reported to drug surveillance agencies suggest that interactions with a variety of drugs (particularly cyclosporine in transplant patients) are the most relevant adverse effects of hypericum extracts.

One RCT (Gastpar, Singer et al. 2005) which compared St John's Wort with sertraline found that the effect of both treatments was similar after 12 weeks treatment on all scales. The adverse events of 12 patients in the hypericum group (9.8 %) and of 16 patients in the sertraline group (13.6%) were possibly related to study medication. No basic differences in the treatment groups were observed and no interaction with concomitant medication was documented.

***Response at 12 weeks***

<b>Scale</b>	<b>Hypericum</b>	<b>Sertraline</b>
Hamilton depression scale (mean ± SD)	8.3 ± 5.5	8.1 ± 5.6
Von Zerssen's Adjective Mood Scale (mean ± SD)	19.8 ± 13.7	21.4 ± 16.3
Clinical Global Impression (% improvement)	68.7%	63.2%

One other RCT (Randlov, Mehlsen et al. 2006) which compared two doses of St John's Wort extract with placebo in participants with mild/moderate depression or dysthymia found no significant difference in the three groups for all measures except for the Beck depression inventory in the non-dysthymia group (p = 0.045). When an ad hoc analysis was performed combining both St John's Wort treatments for the non-dysthymic group, there was a significant difference in the reduction in the Hamilton score to < 7 (p = 0.030) and reduction in the Beck's depression inventory > 50% (p = 0.030) but not on the reduction in Hamilton score > 50% (p = 0.175). There was no significant effect in the dysthymic group on any score.

Side effects were reported in 39 patients (10 on the high-dose, 16 on the low-dose and 13 on placebo;  $p=0.707$ ). Side effects were mild, mainly headache and gastrointestinal symptoms and did not require stopping the medication.

Another RCT (Szegedi, Kohlen et al. 2005) comparing St John's Wort (WS 5570) with paroxetine found a decrease in the Hamilton depression scores over 6 weeks by an average of 14.4 (SD 8.8) for St John's Wort and by 11.4 (SD 8.6) for paroxetine. This difference was reported as statistically significant. Also, at the end of the acute treatment phase (6 weeks), 71% in the St John's Wort group and 60% in the paroxetine group responded to treatment ( $p=0.08$ ) and 50 % and 35% of patients respectively showed remission ( $p=0.02$ ). The results of the other scales used supported this finding.

Fifty-five percent of patients in the St John's Wort group and 76% in the paroxetine group experienced adverse events. Two serious events were recorded in the St John's Wort group but these were not considered to be a result of the treatment.

	<b>St John's Wort</b>	<b>Paroxetine</b>	<b>P value</b>
Decrease in the Hamilton depression scale	14.4	11.4	reported as statistically significant
Responded to treatment	71%	60%	$p=0.08$
Remission	50 %	35%	$p=0.02$
Adverse events	55%	76%	Not given

Another RCT (Bjerkstedt, Edman et al. 2005) comparing St John's Wort (LI160) with fluoxetine and placebo found a reduction in the Hamilton depression scale of between 35-40% without any significant differences between treatments. The same was found for all other scales except remission (final Hamilton depression score  $< 8$ ) where both St John's Wort (24%) and fluoxetine (28%) were significantly better than placebo ( $p=0.02$  and  $0.005$  respectively)

There were 116 adverse events in 69 participants. There were significantly higher adverse events in the fluoxetine group compared to the St John's Wort group ( $p=0.04$ ) and the placebo group ( $p=0.01$ ).

An RCT performed in Germany (Fava, Alpert et al. 2005) comparing St John's Wort (LI160) with fluoxetine and placebo found that treatment with St John's Wort was associated with a significantly ( $p<0.05$ ) greater decrease in the Hamilton depression score compared to fluoxetine (except at week 8). However, there was no significant difference between St John's Wort and placebo or between fluoxetine and placebo on any measure. The study was under-powered and had a large drop-out rate which may explain this unexpected finding.

Another RCT (Uebelhack, Gruenwald et al. 2004) comparing St John's Wort (STW 3-VI) with placebo found the Hamilton depression score decreased significantly in the St John's Wort group compared to the placebo group ( $p=0.001$ ). Comparable differences were found for the St John's Wort group for all other assessment scales.

Twenty-three adverse events were reported by 21 participants. In the St John's Wort group, 16 adverse events (22.9%) were seen in 14 patients (12 'mild' and 4 'moderate'). Only 2 events were considered to be related to St John's Wort. In the placebo group, adverse events were seen in 7 (10%) of patients (6 'mild' and 1 'moderate').

### **11. Discussion of Findings**

There is good evidence that St John's Wort improves symptoms of mild to moderate depression. These people may not meet the criteria for major depression. The beneficial effects of St John's Wort have been demonstrated in a systematic review of studies comparing this treatment to placebo and standard antidepressant treatment. Another two RCTs confirmed that St John's Wort was more effective than placebo and one confirmed that St John's Wort was as effective as a standard antidepressant. This finding was not supported by another RCT but this can be perhaps explained by the study being under-powered.

For major depression the evidence is inconclusive. The systematic review found a small benefit compared to placebo. One RCT found that St John's Wort was as effective as a standard antidepressant. Another supported this finding but could not demonstrate a benefit for St John's Wort or the standard antidepressant over placebo. This could be explained by poor methodological quality and a drop out rate of 47%.

There is good evidence that St John's Wort extracts caused fewer side-effects than older antidepressants but a similar number to selective serotonin reuptake inhibitors.

Many patients buy St John's Wort products from health-food stores and might not disclose this to their doctors. This can be problematic, because serious interactions can occur with a number of frequently used drugs <http://www.medsafe.govt.nz/Profs/PUarticles/sjw.htm>

The quality of Hypericum preparations can also differ considerably, and a number of products contain only minor amounts of bioactive constituents.

More studies that compare specific extracts with both placebo and standard antidepressants in clearly defined patient populations with and without major depression are needed.

## 12. Conclusions

There is level 1 evidence that St John's Wort is effective for mild or moderate depression.

There is level 4 evidence that St John's Wort may be effective for major depression.

There is no evidence about effectiveness in severe depression.

There is level 2 evidence that St John's Wort extracts caused fewer side-effects than older antidepressants but a similar number to selective serotonin reuptake inhibitors.

St John's Wort extracts can have serious interactions with a variety of other drugs

## 13. References

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