



Access Economics Report: St.John's wort for depression

August 2010

Report by Access Economics Pty Limited for

The National Institute of Complementary
Medicine

3 St John's wort for depression

3.1 Background

St John's wort refers to the plant species *Hypericum perforatum*. Some 370 species of the genus *Hypericum* exist worldwide and extracts of 'common' St John's wort (*H. perforatum*) can be quite heterogenous²⁶. St John's wort has been used since ancient Greek times as a herbal treatment for depression (and as an anti-inflammatory and antiseptic). A Cochrane review by Linde et al (2008) found that:

'The available evidence suggests that the hypericum extracts tested in the included trials a) are superior to placebo in patients with major depression; b) are similarly effective as standard anti-depressants; and c) have fewer side effects than standard anti-depressants.'

*St John's wort*²⁷



Rahimi et al (2009) in a systematic review of St John's wort and SSRIs similarly found St John's wort to be as effective as selective serotonin reuptake inhibitors (SSRIs). Both studies found that St John's wort was associated with fewer patient withdrawals from treatment due to adverse events. Although non-toxic to humans in these doses, in large quantities St John's wort is poisonous to grazing livestock.

St John's wort is available over the counter in most countries with extracts usually in tablets or capsules, but also as a tea or in other forms. The exact mechanism for the anti-depressant effects of St John's wort is unclear, and available research indicates that several components are relevant. Its anti-depressant mechanism is believed to involve inhibition of serotonin (5-HT) reuptake, similar to conventional SSRIs, with the major constituents thought to be hyperforin and hypericin (Leuner et al, 2007).

3.2 Aim

The aim of this study is to undertake a cost effectiveness analysis of St John's wort compared with standard anti-depressants – tricyclic anti-depressants (TCAs), SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) etc – for mild to moderate (not severe) depression.

3.3 Indication

The general lay term 'depression' is often used to describe the clinical condition of 'major depression'²⁸ as defined and classified in the Diagnostic and Statistical Manual of Mental Disorders (developed by the American Psychiatric Association). Depression is a mood disorder characterised by low mood and self-esteem, loss of interest or pleasure in normally enjoyable

²⁶ St John's wort refers to more than one commercial product and the results of this paper are based on products used in published clinical trials.

²⁷ Photo source: http://en.wikipedia.org/wiki/St_John%27s_wort

²⁸ Also known as 'major depressive disorder', 'clinical depression' or 'unipolar depression/disorder'.

activities, and adverse functional impacts on a person's family, work or school life, sleeping and eating habits, and general health. Diagnosis of depression is based on the patient's self-reported experiences, behaviour reported by relatives or friends, and a mental status exam.

3.3.1 Epidemiology

Prevalence

A literature search was conducted to find estimates of the prevalence of mild to moderate depression. The search terms were “Prevalence depression” and “prevalence AND epidemiolog* AND depress* AND Australia”. The NCBI and NIH Pubmed databases were searched in August 2009 and selection criteria included articles: (1) in English; (2) published in the last five years; and (3) concerning studies in humans. Findings are summarised in Table 3.1.

The results of the Australian National Survey of Mental Health and Wellbeing conducted in 2007 (ABS, 2008) suggested that the one year prevalence of depression in adults was 3.1% among males and 5.1% among females. Mild, moderate, and severe categories were not reported separately. According to both Kessler et al (2005) and Bierut et al (1999), an approximate proportion of those with severe depression is 30.9%, suggesting prevalence of moderate to mild depression among males of 2.14% and among females of 3.52%.

Depression, like anxiety, often remains sub-optimally treated or untreated, with the Survey of Disability Ageing and Carers reporting that 56% of people with clinical depression received any form of professional care (ABS, 1998).

Mortality

In 2007 there were 0.26 deaths per 100,000 people with a depressive episode as the underlying cause (ABS, 2009a). The available data do not allow a distinction between deaths from mild to moderate versus severe depression.

Table 3.1: Epidemiology of depression

Source	Aim and method	Definitions	Findings
ABS (2008) (Australia)	<p>The National Survey of Mental Health and Wellbeing conducted in 2007 surveyed Australians in private dwellings and reported prevalence of depression in those aged 16 to 85 years. Face to face interviews with 8,841 fully-responding households, representing a 60% response rate.</p> <p>The survey used the World Mental Health Survey Initiative version of the World Health Organization's Composite International Diagnostic Interview, version 3.0 (WMH-CIDI 3.0).</p>	Based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Statistical Classification of Diseases and Related Health Problems (ICD-10). ²⁹ Severe, moderate and mild depressive episodes	<p>The lifetime prevalence of depression was 8.8% among males and 14.5% among females.</p> <p>The one year prevalence³⁰ was 3.1% among males and 5.1% among females.</p> <p>Mild/moderate/severe depression were not reported separately.</p> <p>Data for depressive episodes were not reported by age.</p>

²⁹ As Linde et al (2008) note, there are two major classification systems to diagnose depressive disorders, the DSM and ICD. DSM-IV defined depressive diagnoses to include recurrent or persistent major depression and minor depression. ICD-10 diagnoses (codes F32 and F33 (WHO 2007)) include recurrent or persistent depression with mild, moderate or severe episodes. According to the DSM-IV diagnostic classification, either depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two week period has to be present to diagnose a major depressive disorder. The ICD-10 system uses the term depressive episode instead of major depressive disorder, but lists similar criteria.

³⁰ The proportion of people who experienced relevant symptoms at any time during the preceding 12 months.

Source	Aim and method	Definitions	Findings
Kessler et al (2005) (USA)	To estimate the 12 month prevalence, severity and comorbidity of DSM-IV anxiety, mood, impulse control and substance disorders in the US National Comorbidity Survey Replication which surveyed English speakers in the coterminous US. Face to face interviews in households were conducted over 2001 to 2003. 9,282 English speaking respondents aged 18 yrs or older. Response rate 70.9%.	12 month DSM-IV disorder. Serious= 12 month suicide attempt with serious lethal intent; work disability or substantial limitation due to disorder; positive screening results for non-affective psychosis; bipolar I or II, substance dependence with serious role impairment, impulse control disorder with repeated serious violence or any disorder that resulted in 30 or more days out of role in a year.	12 month prevalence of major depressive disorder = 6.7% (standard error 0.3). In these people: 30.4%(1.7) were serious; 50.1%(2.1) were moderate; and 19.5% (2.1) were mild. Severity by gender not reported. Probably an underestimate of prevalence because those with mental illness less likely to respond, and exclusion of non-English speakers and homeless.
Bierut et al (1999) (Australia)	To examine the genetic and environmental contributions to major depressive disorder in a volunteer community based sample of male and female twins Subjects drawn from NHMRC volunteer sample of twins. Phone interviews conducted in 1992-93 of 2,685 pairs of twins Lay interviewees used Semi-Structured Assessment for the Genetics of Alcoholism instrument	DSM-III R major depressive disorder, DSM-IV major depressive disorder and DSM-IV severe major depressive disorder. DSM-IV major depressive disorder requires cluster of 5 symptoms during at least two weeks plus impairment of functioning or seeking treatment. Severe major depressive disorder requires 6 symptoms during at least 4 weeks.	Lifetime prevalence DSM-IV major depression in 15.7% of males (n=287) and 22.4% of females (n=784) Lifetime prevalence of severe DSM-IV major depression was 3.4% of males (n=63) and 9.2% of females (n=320).

3.4 Intervention

The intervention is St John's wort for the treatment of mild to moderate (not severe) depression, with more detail in Section 3.4.2.

3.4.1 Literature search

A literature search was undertaken on 14 July 2009 of NCBI and NIH Pubmed using search parameters of "St John's wort and depression". Selection criteria were: (1) in English; (2) published after July 2008 (the last search undertaken in Pubmed by Linde et al, 2008); and (3) studies in humans. New studies published after the Cochrane Review by Linde et al (2008) included: Brattström (2009), Rahimi et al (2009) and Kasper et al (2008). A summary of literature reviewed for this study is in Appendix A (Section 3.13). Linde et al (2008:2) reviewed:

'29 studies in 5,489 patients with depression that compared treatment with extracts of St. John's wort for 4 to 12 weeks with placebo treatment or standard antidepressants. The studies came from a variety of countries, tested several different St. John's wort extracts, and mostly included patients suffering from mild to moderately severe symptoms. Overall, the St. John's wort extracts tested in the trials were superior to placebo, similarly effective as standard antidepressants, and had fewer side effects than standard antidepressants. ... Patients suffering from depressive symptoms who wish to use a St. John's wort product should consult a health professional. Using a St. John's wort extract might be justified, but important issues should be taken into account: St. John's wort products available on the market vary to a great extent. The results of this review apply only to the preparations tested in the studies included, and possibly to extracts with similar characteristics. Side effects of St. John's wort extracts are usually minor and uncommon. However, the effects of other drugs might be significantly compromised.'

Rahimi et al (2009) conducted a meta-analysis of the efficacy and tolerability of Hypericum perforatum compared with selective serotonin reuptake inhibitors (SSRIs). Thirteen RCTs were included. The authors found no significant difference in efficacy between Hypericum and SSRIs although the risk of withdrawal from studies due to adverse events was significantly lower with Hypericum.

Kasper et al (2008) investigated the efficacy and safety of hypericum in preventing relapse during 6 months continuation treatment and 12 months long term maintenance treatment after recovery from an episode of recurrent depression compared with placebo. Brattstrom (2009) conducted an open multicentre safety study of Hypericum.³¹

3.4.2 Specification of St John's wort extract

St John's wort products available on the market are not standardised and hence unlikely to be equally effective (Linde et al, 2008; Williams and Holsinger, 2005; Hypericum Depression Trial Study Group, 2002). Trials have tested a variety of extracts and hence the findings of Linde et

³¹ Two 2010 studies were published after most of this analysis was completed, and so were not included, but support the conclusions of this study (Kasper et al, 2010; Melzer et al, 2007).

al (2008) and Rahimi et al (2009) were not based on one homogeneous extract, but on a range of different extracts.

Linde et al (2008) argued that their findings most likely applied to products using ethanol 50% to 60% or methanol 80% for extraction from dried plant material, with daily extract dosages of 500 to 1200 mg with a ratio of raw material to extract of 3-7:1. This in a sense provides a base standard for St John's wort.

Our analysis is based on two St John's wort products available in Australia at a dose of 900mg per day. Both products are extracts of *H. perforatum* equivalent to dry flowering herb top, 1800mg, standardised to contain hypericin 990 mcg. These products were selected using an on-line pharmacy search on the basis that information regarding their formulation was easily accessible and accords with the base standard above, and tablets are easily divisible to provide this daily dose (some tablets identified in the search would need to be cut in thirds or into two-thirds). Also, where one product was available in two sizes, the larger size was selected as it was cheaper per dose – an important factor in consumer's selection of long term medications.

3.4.3 Interactions with other drugs

Both St John's wort and standard anti-depressants can result in adverse side effects when taken in combination with other anti-depressants, and other medications. For example, St John's wort can cause decreased levels of concentration in drugs that are dependent on dose to be effective, e.g. some statins (drugs for high cholesterol), HIV-AIDS, allergies, thrombosis and oral contraceptives (Williams and Holsinger 2005; Piscitelli et al, 2000).³² Standard anti-depressants can also interact with these and other drugs (e.g. drugs for HIV-AIDS, migraine, NSAIDS, and thrombosis and cardiac medications) (Spina et al, 2008; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004). Roughead et al (2007) noted the potential for interactions between anti-depressants and other drugs in the Australian Veteran Population.

Unlike standard anti-depressants, St John's wort is currently available without medical supervision (Hammerness, 2003; Whitten, 2006). Physicians are therefore recommended to regularly ask their patients about the use of products containing hypericum (Rahimi et al, 2009).

3.4.4 Side effects and adherence

The literature suggests that St John's wort is associated with marginally fewer adverse events than standard anti-depressants, but this was not statistically significant.

However, patient withdrawals from clinical trials of St John's wort due to adverse events are significantly less than patient withdrawals from clinical trials of standard anti-depressants (Linde et al, 2008; Rahimi et al 2009 for SSRIs and Appendix B in Section 3.14).

For the purposes of cost effectiveness analysis, it is difficult to determine the impacts of the specific adverse events on health system costs and quality of life because:

³² Interactions with these drugs does not occur for all St John's wort extracts (e.g. low hyperforin extracts have few if any substantial interactions). Drug interactions occur frequently between conventional drugs and this does not preclude their use, but means clinicians must be aware and either avoid or titrate doses accordingly.

- there is a potentially wide range of adverse events for both St John's wort and standard anti-depressants (e.g. Ferguson 2001 summarises the side effects of standard anti-depressants) and there is inconsistency across studies on the range of adverse events reported. For example, HDTSG (2002), Szegedi et al (2005) and van Gulp et al (2002) all published findings for a different selection of adverse events.
- serious adverse events e.g. deaths from serotonin syndrome or an injurious fall at work as a result of SSRI discontinuation syndrome are either too few to measure or without available data.
- there is little evidence on the long term/lifetime health impacts associated with adverse events from St John's wort or SSRI/anti-depressant use. There are no sources which make a direct comparison of long term impacts between St John's wort and pharmaceutical anti-depressants.

Odds ratios for discontinuation of treatment (or 'drop out' rates) because of adverse events and more broadly, drop out rates for any reason, were calculated by Linde et al (2008) based on five RCTs of older anti-depressants compared with hypericum and 11 RCTs of SSRIs compared with hypericum.

- Compared with standard anti-depressants, the odds ratio (OR) of dropping out from the hypericum group because of adverse events was 0.41 (95%CI 0.29 to 0.60).
- Compared with standard anti-depressants, the OR of dropping out of the hypericum group for any reason (including loss to follow up, insufficient/inadequate response, adverse events or protocol violation) was 0.77 (95% CI 0.62 to 0.95).

Reasons other than side effects for non-adherence can include the long duration of treatment and a lack of understanding of the importance of persisting with therapy in order to receive the benefits. Differences in adherence are important in cost effectiveness analysis as low adherence can incur costs but reduce efficacy.

For this analysis, adherence with St John's wort is similar to that of anti-depressants reflecting the findings of Müller et al (2004), Szegedi et al (2005) and Van Gulp et al (2002). However the protective ORs for dropout rates are modelled in the sensitivity analysis.

3.5 Comparator

There are currently no National Health and Medical Research Council (NHMRC) guidelines for treatment of depression.³³ According to the Royal Australian and New Zealand College of Psychiatrists (2005) guide for consumers and carers, initial treatment for depression by a GP should include one or some combination of:

- referral to a psychiatrist or other health professional or hospital;
- anti-depressant medication and cognitive behavioural therapy/interpersonal psychotherapy;
- weekly checkups with a GP or another health professional.

³³ NHMRC Guidelines on treatment of depression in young people published in 1997 were rescinded in 2004 following the NHMRC's standard five-year publication review.

Following this, patients should visit their GP not less often than every six weeks to have a symptom review, a review of changes in problems and supports and a review of treatment side effects. Treatment may then be adjusted. Discussion of medications suggests that:

- SSRIs would generally be first line treatment because side effects are less common than with TCAs or venlafaxine;
- TCAs are more likely to be used if the depression is severe and or another treatment has not worked sufficiently. Side effects of TCAs are more common than with SSRIs; and
- Venlafaxine (SNRI) is useful when other treatments have been unsuccessful or for severe depression.

Hence the comparator is defined as treatment with standard anti-depressants available in Australia (as per Table 3.2).

The Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression (2004) recommend cognitive behavioural therapy/interpersonal psychotherapy or SSRIs as first line monotherapy for moderate depression. If there is either partial or no response to an SSRI as first line therapy, second line therapy involves a switch to TCA or Venlafaxine, with the addition of cognitive behavioural therapy. Partial or non-response to second line therapy would then involve augmentation and combination. Changes in dose at any stage may also be considered.

SSRIs were the most commonly used anti-depressant in Australia in 2006, although tricyclics and other anti-depressants were not uncommon (Table 3.2). In 2006, Sertraline (an SSRI) was the ninth most commonly dispensed drug of all in the Australian community (adjusted for differences in quantity per prescription and daily dose) (Australian Government Department of Health and Ageing, 2006).³⁴ Out of all the classes of anti-depressants, SSRIs had the highest average use (adjusted for differences in quantity per prescription and daily dose) (Table 3.2).

Table 3.2: Community scripts for anti-depressants, 2006

Type of anti-depressant	Number scripts dispensed	Defined daily dose/1,000 people/day (average)
Tricyclics	3,005,095	0.9
SSRIs	7,983,057	7.7
Monoamine oxidase inhibitors	220,491	0.6
Other	3,321,882	3.3

Source: Australian Government Department of Health and Ageing (2006).

Approach to treating patients who discontinue therapy because of side effects or inadequate response to treatment

The guidelines do not specify an approach to treating patients who discontinue therapy because of side effects or inadequate response to treatment. If a patient discontinues treatment, his or her GP or psychiatrist would be concerned about the potential for the condition to deteriorate leading to a possible adverse event (discontinuation syndrome,

³⁴ In terms of defined daily dose per 1,000 population per day.

hospitalisation or self harm). The health professional may encourage the patient to remain on the drug at a higher dose to see if the response improves, or the same dose to see if the side effects are a short term phenomenon and dissipate in the medium term. If this approach is not successful, the health professional may then consider switching the patient to another anti-depressant medication. Switching is associated with the danger of both serotonin syndrome, and discontinuation syndrome, and so it is likely that switching would be undertaken gradually over a number of weeks, with medical oversight.

3.6 Effectiveness

Based on double blind randomised controlled trials in adults with mild to moderate depression,³⁵ Linde et al (2008) found that St John's wort was as effective as standard treatment, with fewer side effects (but with statistically insignificant difference in risk). Rahimi et al (2009) made similar conclusions in their systematic review comparing St John's wort with SSRIs. These two studies together covered all the RCTs from the literature review except the predominantly German studies – Brattstrom et al (2009) and Kasper et al (2008). Linde et al (2008) found that trials from German-speaking countries reported findings more favourable to hypericum.³⁶ These two studies, however, were primarily safety focused and also supported the results from the higher quality meta-analysis and systemic review.

Rahini et al (2009) concluded that: "hypericum does not differ from SSRIs according to efficacy and adverse events in major depressive disorder" and Linde et al (2008) concluded that "trials of hypericum and standard antidepressants were statistically homogenous".

Based on the findings of Linde et al (2008) and Rahimi et al (2009), the modelling applies the same efficacy for St John's wort and standard anti-depressants.

3.7 Benefits

Ideally the benefits of this study would be reported in DALYs, with benefits measured in terms of the efficacy of the intervention (St John's wort) and comparator (SSRIs) as well as DALYs lost from the adverse event profiles of the two arms.

However, since the conclusion was equal efficacy and safety, benefits of the two arms from efficacy and adverse events are treated as comparable in the model. In incremental terms this means there is no difference between the intervention and the comparator in relation to DALYs averted that are able to be measured on the basis of current evidence for these two health outcomes.

However, as discussed above, switching may occur under the comparator arm and the costs of this include DALY impacts, as estimated in Section 3.9. This is included in the sensitivity analysis.

³⁵ Evidence on SJW for severe depression insufficient so findings only apply to adults with mild to moderate depression (Linde et al 2008).

³⁶ Extracts of St. John's wort are licensed and widely used in Germany for the treatment of depressive, anxiety and sleep disorders (Linde et al 2008).

3.8 Model

A decision tree model was used and the method for the cost effectiveness analysis was incremental, i.e. the costs of St John’s wort were compared with the costs of SSRIs.

The choice of key parameters for costs is outlined in the section below.

3.9 Costs

3.9.1 Direct cost of treatment

For this analysis, it was assumed that St John’s wort would be taken under the same medical supervision as pharmaceutical anti-depressants, consistent with standard care for depression. Depression is a serious disease, and both standard antidepressants and St John’s Wort can interact with other drugs. Thus, the only difference in unit health system costs in this analysis relates to the unit costs of St John’s wort and standard anti-depressants. Other health system costs such as GPs, psychologists or psychiatrists providing cognitive behaviour therapy or interpersonal therapy, are the same for patients whether taking St John’s wort or standard anti-depressants.

The estimated cost to the Australian Government of anti-depressants dispensed to Australians in 2007-08 was \$0.55 per day (AIHW, 2009)³⁷ — **in 2009, approximately \$0.57 per day** (AIHW, 2008).³⁸ Notably, this does not include the patient copayments which were \$5.00 (concession) and \$31.30 per script in 2008. However, no data were found on the average patient copayment for anti-depressants, although in other (unpublished) analysis, Access Economics has found that for long term medications, gaps are relatively small in percentage terms due to safety nets.

The **average cost per day of St John’s wort (at a dose of 900mg per day) in 2009 was \$0.17** (an average of the daily cost of \$0.13 and \$0.17 in Table 3.3).

Table 3.3: Retail cost of St John’s wort

Tablets per bottle	Dose per tablet*	Ingredient	Cost per bottle	Cost per day
60	1800mg	990 mcg hypericin	A\$15.95	\$0.13
90	1800mg	990 mcg hypericin	A\$35.95	\$0.20

Source: <http://www.pharmacyonline.com.au/> accessed 10 September 2009. * Hence half a tablet per day.

3.9.2 Cost of changing treatment due to side effects or non response

Khandker et al (2008) found that patients with depression who are resistant to treatment and switch medications had higher all cause and depression related pharmaceutical and medical related costs than non switching patients after controlling for comorbidities. This study is not directly comparable to Australia because of differences in the US and Australian health

³⁷ Based on 1,494,587 Australians on anti-depressants in that year and Australian Government expenditure on anti-depressants of \$301.1 million (AIHW 2009).

³⁸ Average annual health inflation between 1996–97 to 2006–07.

systems and also because it is not clear that indicated patients had mild to moderate depression — a proportion may have had severe depression.

A reasonable assumption for this analysis is that patients who drop out would incur at least one additional visit to a clinician (GP or psychiatrist) and would have experienced some diminution of their quality of life whilst switching to a different treatment. The Medicare cost is \$63.75 for the GP visit³⁹ with an average patient contribution of \$4.60⁴⁰ (\$68.35 per visit in total).

A two week period of washout and changeover is assumed. In terms of the impact on the disease burden experienced by those who withdraw from treatment due to adverse events, it is assumed that they experience a return of, or exacerbation of depression whilst not taking medication, so the DALY weight for depression is applied for a length of two weeks.

The same costs are applied to those who drop out in both arms of the analysis (i.e. to St John’s Wort as well as to standard antidepressants) — it is just the rate of drop out from treatment that differs (as explained earlier based on evidence from the systematic reviews by Linde et al, 2008 and Rahimi et al, 2008). The cost estimates discussed here are probably conservative (for example those who experienced side effects great enough to drop out of treatment would experience some diminution of quality of life while on that treatment as well as during the switching period).

3.9.3 Years of healthy life lost due to disability (YLD)

DALY weights are used to adjust a year according to the extent of disease burden experienced. Zero represents perfect health and one represents death.

The disability weight for mild depression is 0.14 and for moderate depression is 0.35 (Mathers et al, 1999). Using proportions of mild and moderate depression from Kessler et al (2005), the weighted average YLD weight is 0.291. Assuming depression is experienced for two weeks while treatment changes, the YLD is 0.011.

3.9.4 Parameter summary

A summary of the parameters used in the analysis of St John’s wort versus standard antidepressants for depression is in Table 3.4.

Table 3.4: Parameters used in the cost effectiveness analysis

Parameter	Sources and methods	Estimate
Efficacy	Linde et al (2008) and Rahimi et al (2009)	Standard anti-depressants and St John’s wort have similar efficacy

³⁹ Medicare Benefits Schedule July 2009 item 36 – a level ‘C’ attendance covering a more detailed history and examination.

⁴⁰ Medicare statistics, Department of Health and Ageing, Table B6a, Medicare average patient contribution per service patient and bulk billed services out of hospital only, June 2009.

OR of dropping out due to adverse events	Linde et al (2008) — OR of discontinuing treatment/dropping out due to adverse/side effects Linde et al (2008) OR of drop out for any reason (including loss to follow up, insufficient/inadequate response, adverse events or protocol violation)	OR favouring hypericum was 0.41 (95%CI 0.29 to 0.60) OR favouring hypericum 0.77 (95% CI 0.62 to 0.95)
Cost of dropping out	Medicare Benefits Schedule July 2009 item 36 – a level ‘C’ attendance covering a more detailed history and examination and average patient contribution for non-referred attendances to GPs from Department of Health and Ageing, Medicare Statistics, Table B6a, June 2009. YLD from Mathers et al 1999 and distribution of depression from Kessler et al 2005.	\$68.35 for a visit to a GP and YLD of 0.011.
Cost of anti-depressants	In 2007-08, anti-depressants were dispensed to 1,494,587 patients, at a cost to the Australian Government of \$301.1 million (AIHW 2009) ⁴¹ .	Cost to the Australian Government per patient per day in 2009 of \$0.57.
Cost of St John’s wort	Australian Pharmacy Online, ⁴² average price for bottles of 1800mg St John’s wort hypericin 990mcg. Dose of 900mg per day.	In 2009, \$0.17 per patient per day.
One year prevalence of mild to moderate depression	ABS (2009) one year prevalence of mild, moderate and severe depression — males 3.1% and females 5.1%. Kessler et al (2005) and Bierut et al (1999) proportion of those with severe depression — 30.9%.	Males 2.14% and females 3.52%
Mortality	ABS (2009) standardised death rates for depressive episodes ICD-10 F32 (zero deaths reported for F33).	In 2007 there were 0.26 deaths per 100,000 people with a depressive episode (mild, moderate or severe) as the underlying cause.

3.10 Results

The cost effectiveness analysis compares St John’s wort with standard anti-depressants assuming equivalence of efficacy and health outcomes, with cost thus being the major determinant of cost effectiveness.

⁴¹ Tables 11.6 and 14.11

⁴² <http://www.pharmacyonline.com.au/> accessed 10 September 2009.

The per person difference is thus $\$0.57 - \$0.17 = \$0.40$ per day, or $\$146.00$ per annum. **St John's wort is cost-saving compared with standard anti-depressants.**

From ABS (2009) above and demographic data, there are an estimated 878,003 Australians with depression of which 69.1% have mild and moderate depression and 56% (ABS, 1998) are treated, a total of 339,752 people.

With treated mild and moderate depression estimated to affect 339,752 Australians in 2009, there could be around $339,752 * 146 = \$50$ million per annum in potential savings from switching to St John's wort from standard anti-depressants.

Due to the finding of comparable health benefits, the results of St John's wort being cost saving compared to standard anti-depressants are naturally highly sensitive to price. The price margin for standard anti-depressants is estimated here as quite substantial – 3.35 times the price of St John's wort. However, it is possible that St John's wort might be more expensive if, for example, there was wastage from pill-halving (albeit pill-cutters are readily available in Australia and cost around $\$12$)⁴³, or if the product was subject to a regulatory regime that aimed to standardise active compounds, extraction processes etc. However, even tripling the price of St John's wort would leave the intervention cost saving.

The major uncertainty is in relation to additional health benefits from St John's wort relative to standard anti-depressants due to the potential cost of changing treatment due to side effects or non-response to stand anti-depressants. The sensitivity analysis including impacts of changing treatment shows that St John's wort would become dominant relative to standard anti-depressants, saving $\$50$ million in costs per annum and 49 DALYs per annum (Table 3.5). The additional GP costs are only $\$0.3$ million of the $\$50$ million total.

Table 3.5: Incremental sensitivity analysis, St John's wort versus standard antidepressants

1. Cost of ADs per day (average)	\$0.57
2. Cost of SJW per day (average)	\$0.17
3. Difference per day (2.-1.)	\$0.40
4. Difference per annum (3.*365)	\$146.00
5. Australians with depression 2008 (ABS, 2009)	878,003
6. % severe (Kessler et al 2005, Bierut et al 1999)	30.90%
7. % on medication (SDAC, ABS 1998)	56%
8. Target group for savings (5.*(1-6.)*7.)	339,752
9. \$m saved pa (4.*8./1,000,000)	\$49.6
10. Ratio of cost (1./2.)	3.35
11. OR drop out any reason (Linde et al 2008)	0.77
12. GP visit cost (MBS Item 36+copayment)	\$68.35
13. Extra disability weight, treatment change (Mathers et al, 1999)	0.011
14. % chance of drop out overall (Brattstrom, 2009)	5.7%
15. No. dropout with ADs (8.*14.)	19,366
16. No. dropout with SJW (11.*15.)	14,912

⁴³ <https://secure.visionaustralia.org/visionaustralia/onlineshop/ProductDetail.aspx?ID=231>

17. Difference (15.-16.)	4,454
18. Cost difference \$m (17.*12./1,000,000)	0.3
19. Incremental DALY difference (17.*13.)	49.0
20. Incremental cost difference \$m (18.+9.)	\$49.9

Source: Access Economics calculations as detailed in this report. AD=antidepressants. SJW=St John's wort.

In the sensitivity analysis, St John's wort dominated standard anti-depressants for mild to moderate depression because it is cheaper than standard anti-depressants and fewer patients withdraw from St John's wort than from standard anti-depressants. Even if the unit cost of St John's wort was the same as that of standard anti-depressants, St John's wort would remain dominant due to the lower changeover rates compared to standard anti-depressants.

3.11 Conclusions

The cost effectiveness analysis in this report found St John's wort was cost-saving relative to standard anti-depressants in the treatment of mild to moderate (not severe) depression. If the lower rate of drop out from St John's wort relative to standard anti-depressants is taken into account, St John's wort dominated standard anti-depressants (i.e. St John's wort was both cost saving and also resulted in a reduced disease burden).

The exact mechanism for the anti-depressant effects of St John's wort is unclear, and available research indicates that several components are relevant. While the findings of equal efficacy in mild to moderate depression by the systematic reviews of Linde et al (2008) and Rahimi et al (2009) were not based on homogeneous extracts, it is unlikely that all St John's wort products are equally effective. The products available on the market are not identical, so it is difficult to extrapolate from clinical trials directly into community practice.

Standardisation of all St John's wort products might be required before St John's wort could be recommended as an alternative to pharmaceutical anti-depressants for mild to moderated depression. Further, St John's wort is currently sold in Australia with limited therapeutic claims which, importantly, exclude 'depression'. If St John's wort were to be sold in Australia with 'depression' as a therapeutic indication, a higher level of regulatory approval would be required. This may in turn increase the cost of commercial St John's wort products. However, even if the costs of St John's wort and standard anti-depressants were the same, St John's wort would be likely to remain cost effective because it is associated with fewer treatment withdrawals due to adverse events than standard anti-depressants.

Depression is a serious disease, and it may be advisable that St John's wort would need to be taken under medical supervision — the same as for standard antidepressants. In addition, both standard anti-depressants and St John's wort can interact with other medications with potentially serious adverse outcomes. This analysis thus assumed that the other health system costs (GP and psychiatrist visits etc) would be the same for St John's wort and standard anti-depressants. The principal potential for cost savings derived from the lower withdrawal rates from treatment associated with St John's wort, leading to reduced costs of switching medications.

The prevalence of mild to moderate depression among Australian males and females is approximately 2.1% and 3.5% respectively — around 226,100 males and 380,600 females in

2008. This is equivalent to 176,570 years of life lost due to disability in 2008 if these people were depressed for the entire year. Further, if all of these people took anti-depressants, the approximate cost to the Australian Government would be \$122.2 million. This does not include patient copayments.

St John's wort has significant potential to be more cost effective than standard anti-depressants for some patients. Further research into St John's wort (including costs for ensuring product standardisation) would be worthwhile.

3.12 References

- Access Economics (2006) *Breaking point: The economic cost of not adhering to bisphosphonate treatment for osteoporosis*, Report for Roche Products Pty Limited and GlaxoSmithKline, Canberra.
- Australian Bureau of Statistics (2009a) *Causes of Death, Australia 2007*, Cat No 3303.0, March.
- Australian Bureau of Statistics (ABS) (2009b) *National Health Survey: Summary of results, 2007-08*, Cat No 4364.0, May.
- Australian Bureau of Statistics (2008) *National Survey of Mental health and Wellbeing: Summary of results*, October, ABS Cat No 4326.0.
- Australian Bureau of Statistics. (1998). *Survey of Disability, Ageing and Carers, Australia. Summary of Findings*, ABS Cat No 4430.0, .
- Australian Government Department of Health and Ageing (2006) *Australian Statistics on Medicines 2006*.
- Australian Institute of Health and Welfare (2008) *Health expenditure Australia 2006–07*. AIHW Health and Welfare Expenditure Series no 35. Cat No HWE 42, Canberra.
- Australian Institute of Health and Welfare (2009) *Mental health services in Australia 2006–07*. AIHW Mental health series no 11. Cat No HSE 74, Canberra.
- Begg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez AD (2007) *The burden of disease and injury in Australia 2003*. AIHW PHE 82, Canberra.
- Bierut LJ, Heath AC, Bucholz KK, Dinwiddie SH, Madden PAF, Statham DJ, Dunne MP, Martin NG (1999) 'Major Depressive Disorder in a Community-Based Twin Sample Are There Different Genetic and Environmental Contributions for Men and Women?' *Arch Gen Psychiatry*. 56:557-563.
- Bolton JM, Sareen J, Reiss JP (2006) 'Genital Anaesthesia Persisting Six Years after Sertraline Discontinuation' *J Sex Marital Ther* 32:237-330.
- Brattström A, 2009, 'Long term effects of St. John's wort (*Hypericum perforatum*) treatment: A 1 year safety study in mild to moderate depression' *Phytomedicine* 16:277-283.
- Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC (2006) 'Methods for Evaluating Patient Adherence to Anti-depressant Therapy: A Real-World Comparison of Adherence and Economic Outcomes' *Medical Care* 44(4):300-303.
- Clayton A, Keller A, McGarvey EL (2006) 'Burden of phase-specific sexual dysfunction with SSRIs' *Journal of Affective Disorders* 91(1):27-32.
- Csoka A, Bahrack A, Mehtonen O (2007) 'Persistent Sexual Dysfunction after Discontinuation of Selective Serotonin Reuptake Inhibitors' *J Sexual Medicine* 5(1):227-233.

- Ferguson JM (2001) 'SSRI Anti-depressant Medications: Adverse Effects and Tolerability' *Prim Care Companion J Clin Psychiatry* 3(1):22–27.
- Gastpar M, Singer A, Zeller K (2005) 'Efficacy and tolerability of hypericum extract STW3 in long term treatment with a once-daily dosage in comparison with sertraline' *Pharmacopsychiatry* 38:78–87.
- Goodyer I, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, Breen S, Ford C, Barrett B, Leech A, Rothwell J, White L, Harrington R (2007) 'Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial' *BMJ Online* doi:10.1136/bmj.39224.494340.55
- Hammerness P, Basch E, Ulbricht C, Barrette E.P, Foppa I, Basch S, Bent S, Boon H, Ernst E, (2003) 'St. John's Wort: A Systematic Review Of Adverse Effects and Drug Interactions for the Consultation Psychiatrist' *Psychosomatics* July-August 44:271-282.
- Hypericum Depression Trial Study Group (2002) 'Effect of Hypericum perforatum (St John's Wort) in Major Depressive Disorder: A Randomized Controlled Trial' *JAMA* 287(14):1807-1814.
- Kasper S, Gastpar M, Möller HJ, Müller WE, Volz HP, Dienel A, Kieser M (2010) 'Better tolerability of St. John's wort extract WS 5570 compared to treatment with SSRIs: a reanalysis of data from controlled clinical trials in acute major depression' *Int Clin Psychopharmacol.* 25(4):204-13.
- Kasper S, Volz HP, Möller HJ, Dienel A, Kieser M (2008) 'Continuation and long term maintenance treatment with Hypericum extract WS 5570 after recovery from an acute episode of moderate depression--a double-blind, randomized, placebo controlled long term trial' *Eur Neuropsychopharmacol* 18(11):803-13.
- Keene MS, Eaddy MT, Mauch RP, Regan TS, Shah M, Chiao E (2005) 'Differences in compliance patterns across the selective serotonin reuptake inhibitors (SSRIs)' *Curr Med Res Opin* 21:1651-1658.
- Kessler R, Chiu WT, Demler O, Walters E (2005) 'Prevalence, severity and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication' *Archives of General Psychiatry* 62:617-627.
- Khandker R, Kruzikas T, McLaughlin T (2008) 'Pharmacy and medical costs associated with switching between venlafaxine and SSRI anti-depressant therapy for the treatment of major depressive disorder' *J Manag Care Pharm*, 14(5):426-41.
- Leuner K, Kazanski V, Müller M, Essin K, Henke B, Gollasch M, Harteneck C, Müller WE (2007). 'Hyperforin--a key constituent of St. John's wort specifically activates TRPC6 channels'. *FASEB J.* 21(14):4101–11.
- Linde K, Berner MM, Kriston L (2008) 'St John's wort for major depression' *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD000448. DOI: 10.1002/14651858.CD000448.pub3.

- Mathers C, Vos T, Stevenson C (1999) *The burden of disease and injury in Australia*. AIHW Cat No PHE 17, Canberra.
- Melzer J, Brignoli R, Keck ME, Saller R (2010) 'A hypericum extract in the treatment of depressive symptoms in outpatients: an open study.' *Forsch Komplementmed*. 17(1):7-14.
- Montejo-González A.L, Llorca G, Izquierdo J.A, Ledesma A, Bousoño M, Calcedo A, Carrasco J.L, Ciudad J, Daniel E, De la Gandara J, Derecho J, Franco M, Gomez M.J, Macias J.A, Martin T, Perez V, Sanchez J.M, Sanchez S, Vicens E (1997) 'SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients' *J Sex Marital Ther* 23(3):176-94.
- Moreno RA, Teng CT, de Almeida KM, Tavares Junior H (2005) 'Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample' *Rev Bras Psiquiatr*. 28(1):29-32.
- Müller T, Mannel M, Murck H, Rahlfs VW (2004) 'Treatment of Somatoform Disorders With St. John's Wort: A Randomized, Double-Blind and Placebo-Controlled Trial' *Psychosomatic Medicine* 66:538–547.
- Piscitelli S.C, Burstein A.H, Chaitt D, Alfaro R.M, Fallon J (2000), 'Indinavir concentrations and St John's wort' *Lancet* 355:547–548.
- Rahimi R, Nikfar S, Abdollahi M, (2009) 'Efficacy and tolerability of Hypericum perforatum in major depressive disorder in comparison with selective serotonin reuptake inhibitors: A meta-analysis.' *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 33:118–127
- Rosen RC, Lane RG, Menza M (1999) 'Effects of SSRIs on sexual function: a critical review' *J Clin Psychopharmacol* 19:67–85.
- Roughead EE, McDermott B, Gilbert AL (2007) 'Anti-depressants: prevalence of duplicate therapy and avoidable drug interactions in Australian veterans.' *Aust N Z J Psychiatry*. 41(4):366-70.
- Royal Australian and New Zealand College of Psychiatrists (2005) 'Coping with depression', *Australian treatment guide for consumers and carers*, June.
- Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression (2004) 'Australian and New Zealand clinical practice guidelines for the treatment of depression' *Australian and New Zealand Journal of Psychiatry*, 38:389–407.
- Schulz V (2001) 'Incidence and clinical relevance of the interactions and side effects of Hypericum preparations' *Phytomedicine* 8:152–160.
- Sheehan DV, Eaddy M, Sarnes M, Vishalpura T, Regan T (2004) 'Evaluating the economic consequences of early anti-depressant treatment discontinuation: a comparison between controlled-release and immediate-release paroxetine' *J Clin Psychopharmacol* 24:544-548.

- Spina E, Santoro V, D'Arrigo C (2008) 'Clinically relevant pharmacokinetic drug interactions with second-generation anti-depressants: an update.' *Clin Ther* 30(7):1206-27.
- Szegedi A, Kohnen R, Dienel A, Kieser M (2005) 'Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine' *BMJ Online* doi:10.1136/bmj.38356.655266.82
- Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ 'Global burden of depressive disorders in the year 2000' *British Journal of Psychiatry* 184:386-92.
- van Gorp G, Meterissian G.B, Haiek L.N, McCusker J, Bellavance F (2002) 'St John's wort or sertraline? Randomized controlled trial in primary care' *Can Fam Physician* 48:905-912.
- van Tulder MW, Koes BW, Bouter LM (1995) 'A cost-of-illness study of back pain in The Netherlands' *Pain* 62(2):233-40.
- VosT, Mathers CD (2000) 'The burden of mental disorders: a comparison of methods between the Australian burden of disease studies and the Global Burden of Disease study.' *Bulletin of the World Health Organization*, 78:427-438.
- Werneke U, Turner T, Priebe S (2006) 'Complementary medicines in psychiatry' *British Journal Of Psychiatry* 188:109 -121.
- Whitten DL, Myers SP, Hawrelak JA, Wohlmuth H (2006) 'The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials' *British Journal of Clinical Pharmacology* 62:512-26.
- Williams JW, Holsinger T (2009) 'St John's for depression, worts and all', *BMJ USA* 5:154-155.
- Woelk H, Burkard G, Grunwald J (1994) 'Benefits and risks of the Hypericum extract LI 160: drug-monitoring study with 3,250 patients' *J Geriatr Psychiatry Neurol* 7(suppl 1):S34-S38.
- World Health Organization (2007) ICD-10 online
<http://apps.who.int/classifications/apps/icd/icd10online/>

3.13 Appendix A: Detailed summary of literature studies relating to St John’s wort and depression

Table 3.6: Literature on effectiveness of St John’s wort for depression

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Rahimi et al (2009)	<p>Meta-analysis</p> <p>Searched for studies comparing the efficacy and tolerability of Hypericum and SSRIs for major depressive disorder in the period 1966 to June 2008.</p> <p>13 trials selected.</p> <p>All included trials in meta-analysis were randomised and double blinded and patients were diagnosed with major depressive disorder according to DSM-IV or ICD-10 criteria.</p>	<p>Extracts: LI-160, STW3-VI, Iperisan, WS 5570, STW3, Calmigen, Ze 117, LoHyp-57</p>	<p>‘Clinical response’, ‘remission’, ‘mean reduction in HAMD score’, ‘total adverse events’, and ‘withdrawals due to adverse events’ were the key outcomes of interest.</p>	<p>Efficacy of hypericum compared with SSRIs based on 11 trials had Relative Risk (RR) of 0.99 (95% CI 0.91-1.08) (p=0.83). Studies found to be homogeneous.</p> <p>The summary RR for adverse events of hypericum vs. SSRIs (8 trials) was 0.85 with a 95% CI of 0.7–1.04, (P=0.11) and the studies were significantly heterogeneous.</p> <p>A summary RR for withdrawal due to adverse events by hypericum vs. SSRIs (11 studies) was 0.53 (95% CI=0.35–0.82) (p=0.004) and studies were homogeneous.</p> <p>Hypericum does not differ from SSRIs according to efficacy and adverse events in major depressive disorder. Lower study withdrawal due to adverse events by hypericum is an advantage in management of major depressive disorder.</p>

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Kasper et al (2008) (Germany and Sweden)	<p>The efficacy and safety of hypericum in preventing relapse during 6 months continuation treatment and 12 months long term maintenance treatment after recovery from an episode of recurrent depression were investigated.</p> <p>Double-blind, placebo controlled multicenter trial. 426 adults (18-65 yo) out-patients with a recurrent episode of moderate major depression⁴⁴, a 17-item HAM-D total score ≥ 20, and ≥ 3 previous episodes in 5 years participated.</p> <p>Excluded schizophrenia, acute anxiety disorder, adjustment disorder, chronic or psychotic depression, bipolar disorder, acute post-traumatic stress disorder, or substance abuse (except nicotine and caffeine). Patients with increased risk of suicide or previous attempted suicide were excluded and concomitant medical and non-medical anti-depressant treatment were prohibited.</p>	<p>Extracts: WS 5570 (3x300 mg/day) WS[®] 55701 is a stabilized dry extract from St John’s wort, extraction solvent methanol 80%, with a defined contents of 3–6% hyperforin, 0.1–0.3% hypericin, not less than 6% flavonoids, and not less than 1.5% rutin. Coated tablets containing 300 mg of the extract were used.</p> <p>Trial phases included a 1 week washout, followed by 6 weeks acute treatment with WS5570. Responders were then randomised to 26 weeks continuation treatment with either WS5570 or placebo. Those on WS5570 were then rerandomised to either WS5570 or placebo for 52 weeks maintenance treatment. (Continuation placebo group continued with placebo during maintenance treatment phase.)</p> <p>Comparator: placebo</p>	<p>HAM-D, Beck Depression Inventory and CGI</p> <p>Relapse rate during continuation treatment (primary outcome measure)</p> <p>Average time to relapse during continuation treatment</p>	<p>WS 5570 prevented relapse after recovery from acute depression. WS 5570 was not associated with any unexpected drug-specific risks or problems of intolerance. Tolerability in continuation and long term maintenance was at the placebo level.</p>

⁴⁴ ICD-10 F33.0 or F33.1, and DSM-IV 296.3

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Linde et al (2008)	<p>To investigate whether extracts of hypericum are more effective than placebo and as effective as standard anti-depressants in the treatment of major depression; and whether they have fewer adverse effects than standard anti-depressant drugs</p> <p>To be included trials had to be double-blind and randomised. 29 trials met the inclusion criteria.</p> <p>Patients had to suffer from major depression (meeting DSM-IV or ICD-10 criteria). Trials in children (< 16 years) were not eligible.</p> <p>Experimental and control treatments had to be given for at least four weeks.</p> <p>Last searches conducted CCDANTR July 2007 and in Pub-med July 2008.</p>	<p>Extract:</p> <p>The following comparisons were performed:</p> <ol style="list-style-type: none"> 1. hypericum extracts vs. placebo 2. hypericum extracts vs. standard anti-depressants (synthetic anti-depressants (TCA and related anti-depressants, SSRIs, SNRIs). Trials using clearly inadequate synthetic anti-depressants (e.g. benzodiatepines) or a dosage clearly below the lower thresholds recommended in current guidelines (Härter 2003, ICSI 2007) were excluded. 	<p>The most frequently used instrument used for outcome measurement was the Hamilton Rating Scale for Depression (used in all trials).</p> <p>The main outcome measure for assessing effectiveness was the responder rate ratio (the relative risk of having a response to treatment). The main outcome measure for adverse effects was the number of patients dropping out due to adverse effects.</p>	<p>Trials of hypericum and standard anti-depressants were statistically homogeneous. Relative risks (RRs) for tri and related were 1.02 (95% CI, 0.90 to 1.15; 5 trials) and for SSRIs were 1.00 (95% CI, 0.90 to 1.11; 12 trials).</p> <p>St John’s wort patients dropped out of trials due to adverse effects less frequently than those given older anti-depressants (odds ratio (OR) 0.24; 95% CI, 0.13 to 0.46) or SSRIs (OR 0.53, 95% CI, 0.34-0.83).</p> <p>Concluded St John’s wort a) superior to placebo in patients with mild to moderate major depression; b) are similarly effective as standard anti-depressants; c) and have fewer side effects than standard anti-depressants. Note the evidence for severe major depression is still insufficient to draw conclusions.</p>

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Brattstrom (2009) (Germany)	<p>To evaluate the long term safety and effects of St John’s wort.</p> <p>Safety study with 440 out-patients in 35 psychiatric and internal medicine practices in Germany suffering from mild to moderate depression. Patients treated for up to one year.</p> <p>Patients 18 years or older with mild to moderate depression without immediate suicidal ideation met the ICD-10 criteria for depressive episodes (F32.0 and F32.1) or recurrent depressive disorders (F33.0 and F33.1) having a minimum HAM-D score of 16 at both baseline visits.</p>	<p>Extract: Ze 117</p> <p>500mg Ze 117 per day (2 tablets 250mg each per day)</p>	<p>Evaluation criteria were safety (adverse event frequency) and influence on depression — 17-item Hamilton depression rating scale (HAM-D), and the Clinical Global Impression (CGI) scale.</p>	<p>A total of 217 (49.3%) patients reported 504 events. 30 of these events were reported by 30 patients and were possibly or probably related to the treatment. 4 patients reported gastrointestinal disorders and 4 patients reported skin rash. 3 patients reported urticaria/pruritus and 3 reported insomnia.</p> <p>A total of 25 patients (5.7%) discontinued treatment due to adverse events, regardless of a relationship with the study medication.</p> <p>6 patients were non-compliant with treatment.</p> <p>ZE 117 is a safe and effective way to treat mild to moderate depression over long periods of time</p>

Source	Aim and method	Extract and comparator	Outcome measure	Findings
<p>Hypericum Depression Trial Study Group (2002) (included in Linde et al 2008) (Included in Rahimi et al 2009)</p>	<p>To test the efficacy and safety of a well-characterized H perforatum extract (LI-160) in moderately severe major depressive disorder.</p> <p>Double-blind, randomised, placebo-controlled trial, Adult outpatients (n=340) with major depression and a baseline total score on the HAM-D of at least 20.</p>	<p>Extract: LI-160</p> <p>Comparator 1: placebo</p> <p>Comparator 2: Sertraline (Zoloft) an SSRI</p> <p>HP vs placebo with daily dose of H perforatum 900 to 1500 mg</p> <p>Sertraline vs placebo with daily dose sertraline 50-100mg</p>	<p>Change in the HAM-D total score from baseline to 8 weeks; rates of full response, determined by the HAM-D and Clinical Global Impressions (CGI) scores.</p>	<p>Neither sertraline nor hypericum perforatum (LI-160) was significantly different from placebo. The efficacy of sertraline was demonstrated on the secondary CGI-I measure, resulting on average in much improvement, hypericum had no efficacy on any measure.</p> <p>Although not designed to compare sertraline with hypericum, the study showed superiority of sertraline on the CGI-I.</p> <p>Rates of diarrhea, nausea, and sweating (sertraline); anorgasmia (sertraline and hypericum); and frequent urination and swelling (hypericum) all were higher than those of placebo. No serious adverse events were found.</p>

Source	Aim and method	Extract and comparator	Outcome measure	Findings
<p>Moreno et al (2005) (included in Linde et al 2008) (Included in Rahimi et al 2009)</p>	<p>8-week double-blind trial of 72 patients with mild to moderate depression. Patients randomly assigned to receive hypericum perforatum 900 mg/day, fluoxetine 20 mg/day or placebo. Aim was to assess the efficacy and safety of hypericum perforatum in comparison with fluoxetine.</p>	<p>Extract: Iperisan®, Marjan Comparator 1: placebo Comparator 2: Fluoxetine (Prozac, SSRI)</p>	<p>Efficacy measures included the HAM-D scale, the Montgomery-Åsberg Rating Scale, and the Clinical Global Impression. Safety was assessed with the UKU Side Effect Rating Scale</p>	<p>Hypericum perforatum was less efficacious than both fluoxetine and placebo. Both drugs were safe and well-tolerated.</p> <p>There were no differences between the three groups regarding safety measures, including vital signs. Tension, nausea, postural dizziness, menorrhagia and diminished sexual desire were more frequent in the fluoxetine group at week 4. Those side effects tended to diminish with time and only menorrhagia persisted in a higher frequency in the fluoxetine group up the 8th week. At the 8th week, there was a higher incidence of insomnia, headache and diarrhea in the fluoxetine group.</p>

Source	Aim and method	Extract and comparator	Outcome measure	Findings
Szegedi et al (2005) (included in Linde et al 2008) (Included in Rahimi et al 2009)	To investigate the efficacy of hypericum extract WS 5570 (St John's wort) compared with paroxetine in patients with moderate to severe depression. Randomised double blind, double dummy, reference controlled, multicentre non-inferiority trial. 251 adult outpatients with acute depression with total score ≥ 22 on the 17 item Hamilton depression scale.	Extract: WS 5570 Comparator: paroxetine (SSRI) 900 mg/day hypericum extract WS 5570 three times a day or 20 mg paroxetine once a day for six weeks. In initial non-responders doses were increased to 1800 mg/day hypericum or 40 mg/day paroxetine after two weeks.	Change in score on Hamilton depression scale from baseline to day 42 (primary outcome). Secondary measures were change in scores on Montgomery-Åsberg depression rating scale, clinical global impressions, and Beck depression inventory.	In the treatment of moderate to severe depression, hypericum extract WS 5570 is at least as effective as paroxetine and is better tolerated. 69/125 patients randomised to hypericum (55%) reported 172 adverse events and 96/126 treated with paroxetine (76%) reported 269 adverse events. Based on the rate ratio, the incidence of adverse events in the paroxetine group was 1.72 (95% confidence interval 1.42 to 2.10) of the rate observed for hypericum.

Note: Judgement has been exercised in reporting and not all RCTs are tabulated – just those considered of particular relevance.

3.14 Appendix B: Side effects of St John's wort and of SSRIs

3.14.1 St John's wort – side effects

Low doses of St John's wort are generally well tolerated according to Hammerness et al (2003) based on findings from Woelk et al (1994), which saw 2.4% of patients receiving 1.08 mg/day of hypericin reporting adverse events and Schulz (2001) which reported 95 incidents of adverse events out of approximately 8 million people using 1.08 mg/day of hypericin.

With higher doses the frequency of side effects increases. For example, Szegedi et al (2005) found 55% of patients on either 900mg/day or 1800mg/day experienced adverse reaction to hypericum with an incidence per day of exposure of 0.029 for 900 mg/day and 0.039 for 1800 mg/day.

The following are the more common side effects as reported in the literature:

- Allergy (dermatological) and alopecia;
- Photosensitisation;
- Neurological effects i.e. headache, neuropathy;
- Psychiatric effects i.e. anxiety;
- Gastrointestinal (GI) disturbances i.e. nausea, diarrhea; and
- Genitourinary effects i.e. sexual dysfunction.

Interactions with other drugs

When taken in combination with other treatments, St John's wort has multiple interactions which can cause more serious side effects than those which occur with sole St John's wort use. A number of studies such as Hammerness (2003) and Whitten (2006) highlight the potential problems of St John's wort being available 'over the counter' to people already using different medications, without medical consultation.

Serotonin syndrome is caused by an excess of serotonin in the central nervous system which can occur through combination use of SSRIs and St John's wort (Williams and Holsinger, 2005). A patient may experience confusion, agitation, nausea and a lack of co-ordination and there are reports of admissions to hospital as a direct consequence as noted by Hammerness et al (2003).

Hyperforin in St John's wort induces (to varying degrees depending on the extract) the cytochrome system, especially the 3A enzymes and the multidrug resistance transporter P-glycoprotein. More than 40% of prescription drugs are metabolised via the cytochrome 3A system and a significant proportion of the population are medicated by them. St John's wort can cause decreased levels of concentration in drugs used to lower cholesterol (simvastatin), HIV (indinavir), allergies, (fexofenadine), thrombosis (warfarin), and oral contraceptives among others (Williams and Holsinger, 2005). The potentially serious repercussions of this are highlighted by Piscitelli et al (2000) which found, during a clinic trial of healthy patients, a 57% decrease in concentrate of indinavir, an HIV protease inhibitor after St John's wort use. Indinavir is heavily dependent on dose to be effective as an HIV treatment and the reduction of concentration caused by St John's wort would have substantial health impacts for HIV patients using both drugs.