

# St John's wort or sertraline?

## *Randomized controlled trial in primary care*

Gerald van Gurp, MD Greg B. Meterissian, MD, FRCPC Laura N. Haiek, MD, MSC  
Jane McCusker, MD, DRPH François Bellavance, PhD

### ABSTRACT

**OBJECTIVE** To compare the change in severity of depressive symptoms and occurrence of side effects in primary care patients treated with St John's wort (SJW) and sertraline.

**DESIGN** Double-blind, randomized 12-week trial.

**SETTING** Community-based offices of 12 family physicians practising in greater Montreal, Que.

**PARTICIPANTS** Eighty-seven men and women with major depression and an initial score of  $\geq 16$  on the Hamilton Rating Scale for Depression (Ham-D).

**INTERVENTIONS** Patients were randomized to treatment with either sertraline (50 to 100 mg/d) or SJW (900 to 1800 mg/d) in a double-blind fashion. Assessment of depression was done at entry and at 2, 4, 8, and 12 weeks using the Ham-D, the Beck Depression Inventory (BDI), and a questionnaire asking about compliance and side effects.

**MAIN OUTCOME MEASURES** Changes from baseline in Ham-D and BDI scores and self-reported side effects.

**RESULTS** There were no important differences in changes in mean Ham-D and BDI scores (using intention-to-treat analysis), with and without adjustment for baseline demographic characteristics, between the two groups at 12 weeks. Significantly more side effects were reported in the sertraline group than in the SJW group at 2 and 4 weeks' follow up.

**CONCLUSION** The more benign side effects of SJW make it a good first choice for this patient population.

### RÉSUMÉ

**OBJECTIF** Comparer les changements dans la gravité des symptômes de la dépression et la survenance d'effets secondaires chez des patients en soins de première ligne traités avec du millepertuis et de la sertraline.

**CONCEPTION** Une étude aléatoire à double insu d'une durée de 12 semaines.

**CONTEXTE** Les pratiques établies au niveau de la collectivité de 12 médecins de famille exerçant dans le Grand Montréal, au Québec.

**PARTICIPANTS** Un total de 87 hommes et femmes souffrant de dépression majeure et présentant un score initial de  $\geq 16$  sur l'échelle de dépression Hamilton (Ham-D).

**INTERVENTIONS** Les patients ont été divisés au hasard pour recevoir soit un traitement à la sertraline (50 à 100mg/j) ou au millepertuis (900 à 1 800mg/j) selon un mode à double insu. L'évaluation de la dépression a été effectuée au début, puis après 2, 4, 8 et 12 semaines, au moyen du Ham-D, de l'inventaire de dépression de Beck (IDB) et d'un questionnaire concernant la conformité à l'ordonnance et les effets secondaires.

**PRINCIPALES MESURES DES RÉSULTATS** Les changements en fonction du point de repère initial dans les scores Ham-D et IDB et les effets secondaires signalés par les intéressés.

**RÉSULTATS** Il n'y avait pas de distinctions importantes dans les changements enregistrés dans les scores moyens Ham-D et IDB (à l'aide d'une analyse du principe de vouloir traiter), avec et sans ajustement pour les caractéristiques démographiques repères entre les deux groupes après 12 semaines. Un nombre considérablement plus élevé d'effets secondaires ont été signalés dans le groupe traité à la sertraline que dans le groupe traité au millepertuis après 2 et 4 semaines de suivi.

**CONCLUSION** Les effets secondaires plus bénins du millepertuis en font un choix privilégié pour cette population de patients.

*This article has been peer reviewed.*

*Cet article a fait l'objet d'une évaluation externe.*

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## RESEARCH

### St John's wort or sertraline?

**D**epressive disorders are among the most common and debilitating illnesses seen by primary care physicians. In recent years, use of St John's wort (SJW) for treating depression has risen exponentially; annual sales in the United States increased from \$20 million to \$200 million between 1995 and 1997.<sup>1</sup>

Studies evaluating the potential benefits of SJW have been conducted mainly in Europe; most have compared it with placebo and tricyclic antidepressants. In a meta-analysis of 23 randomized clinical trials, reviewers concluded that SJW was better than placebo for treating some depressive disorders.<sup>2</sup> These earlier investigations have been criticized for a variety of shortcomings<sup>3,6</sup>: comparison drugs were prescribed in low doses; none of the trials that compared SJW with another antidepressant lasted more than 4 weeks; and few of the studies used a precise classification system for psychiatric disorders.

A recent US multicentre study of patients in a tertiary care setting with moderate-to-severe chronic major depression lasting on average more than 2 years concluded that SJW was no more effective than placebo.<sup>7</sup> Two later German investigations of severe and moderate depression found SJW to be as effective as imipramine.<sup>8,9</sup> To date, only two published studies have compared SJW with newer antidepressants, such as selective serotonin uptake inhibitors. A German study<sup>10</sup> comparing SJW with fluoxetine concluded that the treatments were equivalent. A smaller pilot study in the United States<sup>11</sup> comparing SJW with sertraline in 30 outpatients with various diagnoses of depressive conditions found no difference in efficacy.

Recommendations for future research involving SJW include conducting studies in primary care settings,

**Dr van Gurp** is a Lecturer in the Department of Family Medicine at McGill University, a community-based family physician, and an emergency physician at St Mary's Hospital Centre in Montreal, Que. **Dr Meterissian** is an Associate Professor in the Department of Psychiatry at McGill University and a psychiatrist at the McGill University Health Centre (Montreal General Hospital site).

**Dr Haiek** is an Assistant Professor in the Department of Family Medicine at McGill University and a family physician at the Montérégie Public Health Directorate.

**Dr McCusker** is a Professor in the Department of Epidemiology and Biostatistics at McGill University and Head of the Department of Clinical Epidemiology and Community Studies at St Mary's Hospital Centre.

**Dr Bellavance** is an Associate Professor in the Service de l'enseignement des méthodes quantitatives de gestion at the École des Hautes Études Commerciales in Montreal.

standardizing doses, extending duration of treatment, using reliable diagnostic criteria for depression, reporting adverse effects in detail, and making comparisons with newer agents under usual clinical conditions.<sup>12,13</sup>

Taking these recommendations into account, we conducted a trial with a primary objective of evaluating the severity of depressive symptoms in patients with major depression (defined by *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV],<sup>14</sup> criteria) who were treated for 12 weeks with SJW or sertraline in a primary care setting. The secondary objective was to compare the occurrence of side effects in the same population.

## METHODS

A prospective, randomized, double-blind design was used. The original study protocol and all subsequent modifications received approval from the Research Ethics Committee of St Mary's Hospital Centre in Montreal, Que.

### Subjects

People aged 18 to 65 years fluent in French or English were eligible to participate if they had been diagnosed with major depression using DSM-IV criteria<sup>14</sup> and had a Hamilton Rating Scale for Depression (Ham-D) score of  $\geq 16$ . Patients were excluded if they were pregnant, lactating, not using acceptable contraception, or at serious risk of suicide; had other indications for hospitalization (including delusions or hallucinations); or had a history of drug or alcohol abuse in the previous 3 months, other DSM-IV comorbid conditions, or serious medical illnesses. Patients who had concomitantly used other psychoactive drugs regularly during the previous 2 weeks (4 weeks if taking fluoxetine), with the exception of bedtime sedative-anxiolytics, were excluded.

Initially, subjects were recruited from among the patients of participating doctors. A low recruitment rate during the first 6 months of the study led us to initiate an advertising campaign to acquire more subjects. At the first visit, patients' eligibility was assessed by their physicians in a structured interview. Informed consent was obtained from all eligible patients who agreed to participate.

### Randomization

Eligible subjects were enrolled in the study and referred to a designated pharmacist who dispensed medication to them in the order they arrived using our randomization scheme. Randomization was

done in blocks of 10 using a computer-generated table of numbers.<sup>15</sup> Only the pharmacist, the statistician (F.B.), and the epidemiologist (J.M.) had access to the randomization codes until the end of the study. On completion of the 12-week follow-up visit, patients were given a prescription for sertraline and the brand and dose of SJW used in the study and were instructed to contact the pharmacy to ascertain what treatment they had received. At the request of treating physicians, patients could also be told, after withdrawal from the study, what treatment they had received.

### Data collection

Evaluations took place at entry and at follow-up visits scheduled at 2, 4, 8, and 12 weeks after the initial visit. Instruments used for assessment were the 17-item Ham-D<sup>16</sup> administered by physicians, the self-rated Beck Depression Inventory (BDI),<sup>17</sup> and a self-administered form assessing medication compliance (average number of capsules per day taken during the previous week) and side effects (checklist of 20 symptoms). Sociodemographic data forms were completed by patients at the initial visit. A research assistant collected the questionnaires regularly from doctors' offices.

### Drugs

*Hypericum* extract imported from Germany was obtained in 300-mg opaque capsules from the Swiss Herbal Remedies Company in Richmond Hill, Ont. Independent testing using spectrophotometric analysis<sup>18</sup> confirmed a *Hypericum* content of 0.3%. Sertraline was packaged using identical opaque capsules each containing 16.67 mg of sertraline. Filler was a mixture of 10 parts wheat bran, one part dried parsley, and one part dried tarragon, all ground to a powder, giving the contents a nonspecific herbal colour and odour. Capsules were prepared by the participating pharmacy. Variance in the standard deviation of the capsules' weight was checked and found to be 2% to 3%. Patients were instructed to take one capsule three times daily (a daily dose of either 50 mg of sertraline or 900 mg of SJW).

Participating physicians were instructed that, if at the 4-week follow-up evaluation response to treatment was judged clinically insufficient, the dose should be increased to two capsules three times daily (a daily dose of either 100 mg of sertraline or 1800 mg of SJW).

### Participating physicians

Twelve physicians participated in the study; seven of them had faculty appointments in the Department

of Family Medicine at McGill University in Montreal. All received training from the psychiatrist (G.B.M.) in using the Ham-D with a teaching videotape. During the study, a psychologist under the supervision of the psychiatrist conducted spot checks to promote interrater reliability by attending one patient interview with each participating physician.

### Statistical analysis

A sample size of 30 patients in each group was required to detect an important difference between the groups of 5 points in the change of the mean Ham-D score from enrolment to the 12-week visit. Estimated standard deviation was 6.7,<sup>19</sup> using a 5% two-sided significance level and 80% power.

The primary (intention-to-treat) statistical analysis was an estimation of the difference between treatment groups in change in mean Ham-D scores and the 95% confidence interval of the difference using a two-sided *t* test. Analysis of covariance was also used to compare mean changes adjusting for baseline characteristics. We also used analysis of variance with repeated measures to evaluate the effects of treatment, time, and the interaction between treatment and time, with and without adjustment for baseline characteristics. Missing values were replaced by the closest previous value. The same analyses were repeated for the BDI. We also conducted analyses of data from those who completed the trial; results, not reported here, were similar. Level of significance was set at 5%. All analyses were conducted using SAS software.

## RESULTS

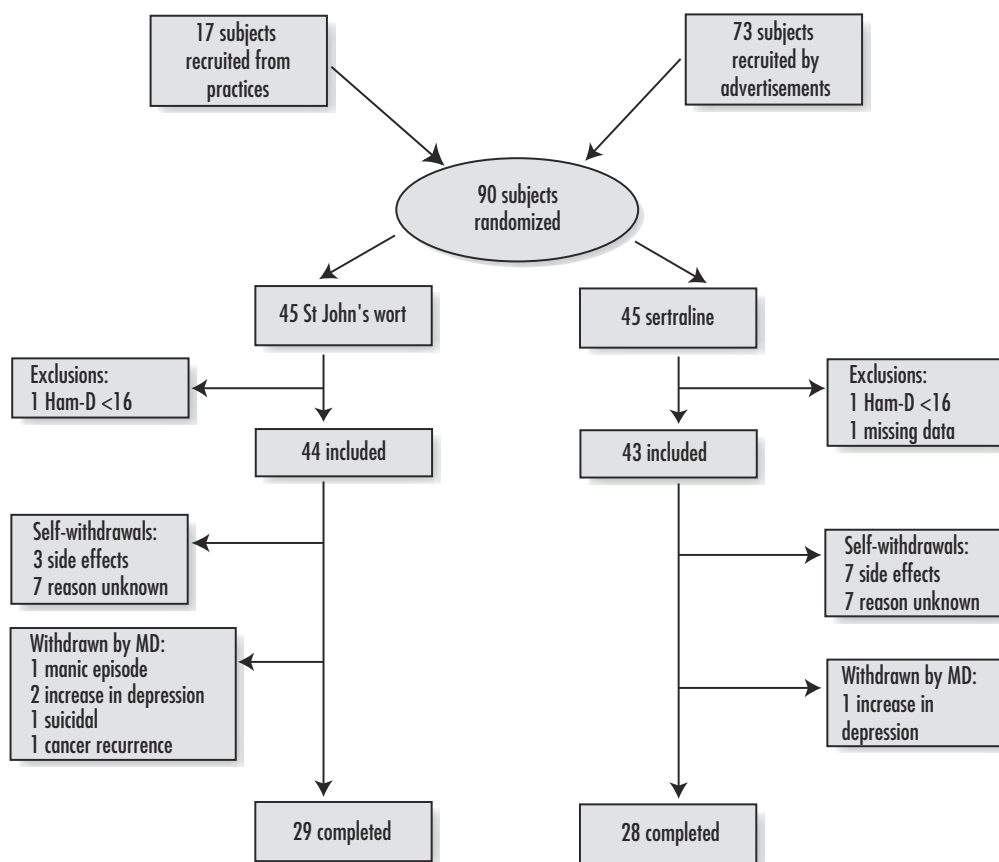
Seventeen patients were recruited from physicians' practices and 73 through advertisements (**Figure 1**). Three patients were excluded, leaving a total sample of 87 subjects, 43 in the sertraline group, and 44 in the SJW group. After withdrawals, 29 SJW and 28 sertraline patients completed the 12-week trial. **Table 1** shows baseline characteristics of the 87 patients by treatment and recruitment source.

Mean Ham-D and BDI scores had declined similarly by 12 weeks in both study groups to about half the mean scores at baseline. There was no significant difference in the decline in both groups in unadjusted and adjusted analyses (**Table 2**). **Figures 2** and **3** show changes over time in mean Ham-D and BDI scores adjusted for the baseline characteristics of the study groups shown in **Table 1**. Results of the two-way analysis of covariance with repeated measures indicated time had a significant effect, but treatment

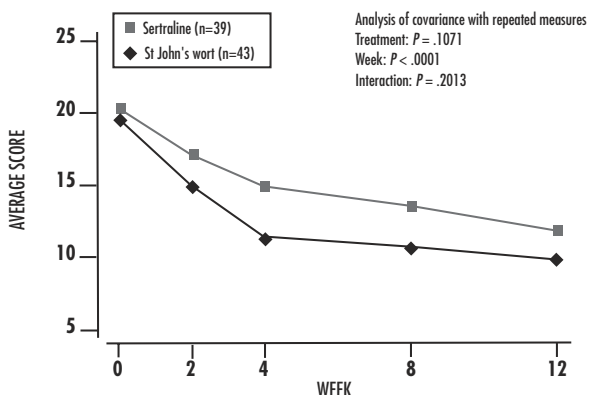
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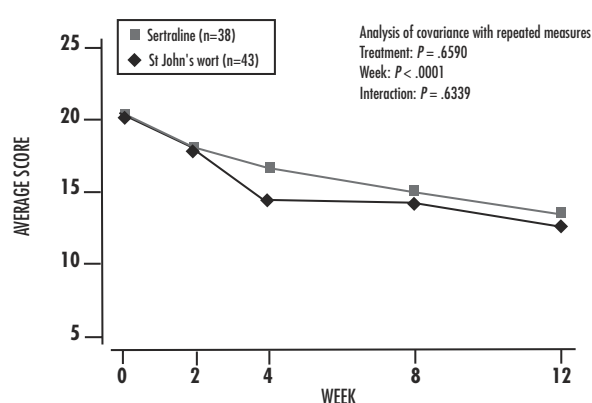
**Figure 1. Study flow chart**



**Figure 2. Changes over time, adjusted for baseline characteristics, on the Hamilton depression scale for all randomized subjects (intention-to-treat analysis): Missing values were replaced by closest previous value.**



**Figure 3. Changes over time, adjusted for baseline characteristics, on the Beck Depression Inventory for all randomized subjects (intention-to-treat analysis): Missing values were replaced by closest previous value.**



**Table 1. Baseline characteristics by study group and recruitment source:** *Mean age of participants ( $\pm$  SD) was 39.1 (10.2) in the sertraline group,\* 40.9 (11.6) in the St John's wort group, 37.9 (11.2) among those recruited through doctor's offices, and 40.5 (10.9) among those recruited through advertisements.\**

CHARACTERISTIC	STUDY GROUPS		P VALUE*	RECRUITMENT SOURCES		P VALUE†
	SERTRALINE (N = 34) N (%)	ST JOHN'S WORT (N = 44) N (%)		DOCTORS' PRACTICES (N = 16) N (%)	ADVERTISEMENTS (N = 71) N (%)	
Sex			.63			.654
• Male	17 (41.5)	16 (36.4)		7 (43.8)	26 (37.7)	
• Female	24 (58.5)	28 (63.6)		9 (56.2)	43 (62.3)	
• Data missing	2	0		0	2	
Marital status			.371			.678
• Married	7 (17.1)	11 (25.0)		4 (25.0)	14 (20.3)	
• Other	34 (82.9)	33 (75.0)		12 (75.0)	55 (79.7)	
• Data missing	2	0		0	2	
Education			.89			.38
• Secondary or less	12 (29.3)	12 (27.9)		6 (37.5)	18 (26.5)	
• Postsecondary	29 (70.7)	31 (72.1)		10 (62.5)	50 (73.5)	
• Data missing	2	1		0	3	
Currently employed?			.007			.63
• Yes	9 (21.9)	22 (50.0)		5 (31.3)	26 (37.7)	
• No	32 (78.1)	22 (50.0)		11 (68.7)	43 (62.3)	
• Data missing	2	0		0	2	
History of depression			.311			.462
• No	11 (27.5)	17 (38.6)		6 (37.5)	22 (32.4)	
• <1 year ago	9 (22.5)	5 (11.4)		1 (6.3)	13 (19.1)	
• >1 year ago	20 (50.0)	22 (50.0)		9 (56.2)	33 (48.5)	
• Data missing	3	0		0	3	
Previous antidepressant use			.35		.145	
• No	22 (53.7)	28 (63.6)		12 (75.0)	38 (55.1)	
• Yes	19 (46.3)	16 (36.4)		4 (25.0)	31 (44.9)	
• Data missing	2	0		0	3	
Duration of current episode			.143			.387
• <6 mo	18 (45.0)	13 (29.6)		7 (46.7)	24 (34.8)	
• $\geq$ 6 mo	22 (55.0)	31 (70.4)		8 (53.3)	45 (65.2)	
• Data missing	3	0		1	2	

\*Information missing for two participants.

†P value of the  $\chi^2$  test.

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and treatment-time interaction effects were not significant for either Ham-D or BDI scores.

The proportion of each group that reported taking at least three capsules daily was significantly higher at 2 weeks in the SJW group than the sertraline group (**Table 3**). Nine patients in each group increased their daily dose to six capsules. Mean number of side effects reported by subjects at 2 and 4 weeks was significantly higher in the sertraline group (**Table 4**). Data on side effects are given in **Table 5**.

## DISCUSSION

Our data indicate that changes in the severity of symptoms in patients with mild-to-moderate depression were similar whether they were treated with SJW or sertraline. Both

groups showed a similar decline to about half the mean baseline Ham-D and BDI scores. It should be noted that the data do not permit us to conclude that the two treatments had equivalent effectiveness. Different assumptions in sample size calculations and a much larger sample would be needed to make such a claim.<sup>20</sup>

These results are consistent with the findings of most previous trials comparing SJW with placebo or other antidepressants.<sup>2,8-11</sup> The contrasting negative results of a recent placebo-controlled trial<sup>7</sup> probably arose from the combined severity and chronicity (mean duration >2 years) of symptoms in patients recruited from a tertiary care setting.

Mean number of side effects reported by those in the sertraline group was significantly higher at 2 and 4 weeks than in the SJW group. This could be associated with our observation that compliance was significantly better in the SJW group at week 2.

**Table 2. Intention-to-treat analysis with last observation carried forward: N = 87.**

SCORE	SERTRALINE MEAN (± SD)	ST JOHN'S WORT MEAN (± SD)	MEAN DIFFERENCE (95% CI)	P VALUE
HAM-D SCORE	(n = 43)	(n = 44)		
Baseline	19.7 (3.5)	18.9 (3.6)	0.8 (-7-2.3)	.285
12 weeks	11.5 (8.4)	9.4 (8.3)	2.1 (-1.4-5.7)	.237
Unadjusted difference	-8.2 (7.5)	-9.5 (7.1)	1.3 (-1.8-4.4)	.402
Adjusted* difference	-8.0 (n = 39)	-8.9 (n = 43)	0.9 (-2.4-4.2)	.582
BDI SCORE†	(n = 40)	(n = 43)		
Baseline	18.4 (5.5)	19.5 (5.0)	-1.1 (-3.4-1.2)	.341
12 weeks	12.0 (8.2)	12.1 (10.1)	-0.1 (-4.2-3.9)	.936
Unadjusted difference	-6.4 (9.4)	-7.4 (8.3)	1 (-2.9-4.8)	.628
Adjusted‡ difference	-6.1 (n = 38)	-6.6 (n = 43)	0.5 (-3.6-4.6)	.808

\*Adjusted for all baseline characteristics presented in **Table 1**. Five subjects had one or more baseline characteristics missing, so they were excluded from the adjusted analyses.

†Scores were missing for four subjects.

‡Five subjects had one or more baseline characteristics missing and one other had only a BDI score, so they were excluded from the adjusted analyses.

**Table 3. Medication compliance by study group: Proportion of subjects taking three or more capsules a week**

WEEK	SERTRALINE N (%)	ST JOHN'S WORT N (%)	P*
2	24/31 (77.4)	33/35 (94.3)	.046
4	26/31 (83.9)	27/33 (81.8)	.828
8	22/23 (95.7)	26/31 (83.9)	.173
12	19/23 (82.6)	23/27 (85.2)	.804

\* $\chi^2$  test for comparison of proportions and t test for comparison of means. P values are unadjusted for multiple tests.

**Table 4. No. of patients reporting side effects by study group: Mean no. of side effects reported by each patient.**

WEEK	SERTRALINE (MEAN NO. OF SIDE EFFECTS ± SD)	ST JOHN'S WORT (MEAN NO. OF SIDE EFFECTS ± SD)	P*
2	31 (4.5 ± 3.2)	35 (2.2 ± 2.5)	.002
4	31 (4.8 ± 4.4)	35 (2.9 ± 3.1)	.038
8	25 (2.8 ± 2.9)	32 (2.2 ± 2.7)	.417
12	25 (3.4 ± 3.6)	29 (1.9 ± 2.4)	.083

\* $\chi^2$  test for comparison of proportions and t test for comparison of means. P values are unadjusted for multiple tests.



**Table 5. Side effects: Week 2 compared with ever during trial**


SIDE EFFECTS	WEEK 2		EVER DURING TRIAL	
	SERTRALINE N (%)	ST JOHN'S WORT N (%)	SERTRALINE N (%)	ST JOHN'S WORT N (%)
Sleep disturbance	11 (35.5)	10 (28.6)	24 (72.7)	23 (54.8)
Anxiety	11 (35.5)	9 (25.7)	18 (54.6)	18 (42.9)
Sexual difficulties	6 (19.4)	2 (5.7)	15 (45.5)	5 (11.9)
Headaches	9 (29.0)	10 (28.6)	14 (42.4)	18 (42.9)
Dizziness	7 (22.6)	3 (8.6)	11 (33.3)	5 (11.9)
Tremor	3 (9.7)	3 (8.6)	5 (15.2)	8 (19.1)
Sweating	8 (25.8)	4 (11.4)	13 (39.4)	7 (16.7)
Dry mouth	14 (45.2)	6 (17.1)	20 (60.6)	16 (38.1)
Muscle spasms	1 (3.2)	1 (2.9)	5 (15.2)	5 (11.9)
Muscle or joint stiffness	5 (16.1)	4 (11.4)	12 (36.4)	8 (19.1)
Urinary problems	3 (9.7)	2 (5.7)	7 (21.2)	7 (16.7)
Difficulty digesting	9 (29.0)	0 (0)	14 (42.4)	8 (19.1)
Nausea or vomiting	12 (38.7)	1 (2.9)	17 (51.5)	4 (9.5)
Diarrhea	14 (45.2)	4 (11.4)	17 (51.5)	10 (23.8)
Lack of appetite	5 (16.1)	4 (11.4)	11 (33.3)	10 (23.8)
Heart palpitations	3 (9.7)	1 (2.9)	7 (21.2)	4 (9.5)
Fatigue	12 (38.7)	8 (22.9)	21 (63.6)	19 (45.2)
Pain	3 (9.7)	3 (8.6)	8 (24.2)	5 (11.9)
Blurred vision	2 (6.5)	3 (8.6)	7 (21.2)	6 (14.3)

Only one serious adverse reaction was reported: a patient taking 1800 mg of SJW required hospitalization after developing an acute manic reaction. Five other cases of mania have been reported.<sup>21,22</sup>

### Limitations

Our investigation has several shortcomings. First, we did not use a placebo-control group because of ethical restrictions. Second, the study population might not be representative of depressed patients in primary care settings. Subjects recruited through advertising differed in several ways from those recruited from primary care practices, as found in previous research.<sup>23</sup> Third, the diagnoses and Ham-D ratings of physicians participating in this trial were not systematically confirmed by a psychiatrist. Nevertheless, most prescriptions for antidepressants are written by family doctors and, given the call for research into SJW in primary care settings "under usual clinical conditions,"<sup>13</sup> this might be viewed as an advantage. Fourth, about one third of subjects did not complete the trial; rates of withdrawal were similar in the two study groups.

### Conclusion

Results of our trial contribute to knowledge of the effectiveness and adverse effects of SJW. Despite the limitations of this investigation, we conclude that, given its favourable side effect profile and apparently similar effectiveness to an accepted antidepressant (sertraline), SJW has a role as first treatment option for mild-to-moderate depression in primary care settings. 

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## RESEARCH

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#### Contributors

All the authors were involved in conception and design of the study, in data collection, and in revising the final draft of the article.

**Dr Meterissian** created the teaching video, helped train the participating doctors and psychologist, and wrote the discussion section of the paper. **Dr McCusker** supervised the randomization of subjects and wrote the results section. **Dr Bellavance** supervised data entry, did the statistical analysis, and prepared the figures.

#### Competing interests

None declared

**Correspondence to:** Dr G. van Gorp, Emergency Department, St Mary's Hospital Centre, 3830 Lacombe Ave, Montreal, QC H3T 1M5; fax (514) 734-2652; e-mail [gerald.vangorp@mcgill.ca](mailto:gerald.vangorp@mcgill.ca)

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#### Editor's key points

- This is the first randomized controlled trial comparing St John's wort with sertraline for treatment of mild-to-moderate depression in a primary care setting with follow up to 12 weeks.
- Improvements in depression scores by 12 weeks were statistically and clinically similar in the two groups.
- St John's wort appeared to have fewer side effects than sertraline at 2 and 4 weeks' follow up. This factor suggests that St John's wort should be considered first in primary care settings.

#### Points de repère du rédacteur

- Il s'agit de la première étude aléatoire contrôlée comparant le millepertuis avec la sertraline pour le traitement de la dépression de légère à modérée dans un milieu de soins de première ligne comportant un suivi pendant 12 semaines.
- Les améliorations dans les scores de dépression après 12 semaines étaient statistiquement et cliniquement semblables dans les deux groupes.
- Le millepertuis semblait avoir moins d'effets secondaires que la sertraline après 2 et 4 semaines de suivi. Ce facteur laisse entendre que le millepertuis devrait être considéré en premier lieu dans des milieux de soins de première ligne.

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