

This MRC Policy Brief summarises the key points of a systematic review evaluating the medicinal use of cannabis. The review was published in June 2015 by Whiting et al. in the Journal of the American Medical Association (JAMA) [1].

Acknowledgements: We are grateful to Dr Penny Whiting, author of the review, who kindly shared her time and expertise in preparation of this MRC Policy Brief.

INTRODUCTION

WHY IS THIS POLICY BRIEF RELEVANT TO SOUTH AFRICA?

- In February 2014 the Medical Innovation Bill was introduced in the South African parliament.
- The Bill includes legalising the medical use of cannabis.
- Further legislation on this issue is likely to come before the national parliament in the future. Up-to-date synthesis of the evidence underpinning the medicinal use of cannabis is required to inform debate and policy-making.

WHAT IS CANNABIS?

- Throughout the ages, many cultures have used cannabis as a medicine.
- Cannabis is a generic term for drugs which are produced from the plant, *Cannabis Sativa*.
- Cannabinoid is the term for the chemicals which can be either derived directly from the cannabis plant or manufactured synthetically.
- The principal active ingredient of cannabis is the cannabinoid: trans-delta -9-tetrahydrocannabinol (THC).
- Cannabidiol (CBD), another cannabinoid, is not psychoactive but is thought to have anti-anxiety and possibly anti-psychotic effects.
- The therapeutic effects of cannabis depends on the concentration of THC in a given formulation as well as the ratio of THC to CBD.
- Cannabinoids can be taken orally, placed under the tongue, rubbed on to the skin, smoked, inhaled, eaten in food, or drunk as a herbal tea.
- Cannabis use is illegal in most countries, including South Africa.
- Estimates of the proportion of recreational users in the South African population vary widely, especially among the adult population. The 2011 SAMRC South African Youth Risk Behaviour survey reported lifetime use of cannabis (ever use) of 19% and 7% for male and female high-school learners in grades 8-11 respectively (with 14% and 5% reporting use in the past 30 days). [2]

MEDICINAL CANNABIS

In some countries cannabinoid-containing medicines can be prescribed by doctors for specific conditions. These medicines include dronabinol and nabilone capsules and oral nabiximol sprays.

In South Africa, no applications to use cannabis as a medicine under Section 21 of the Medicines & Related Substances Act of 1965 have been approved to date.

The number of people using cannabis illegally as a medicine is unknown.

OBJECTIVES OF THE MRC POLICY BRIEF

1. To present the current evidence base for medicinal cannabis by summarising the systematic review results judged to be most relevant to South Africa.
2. To appraise the quality of the systematic review using the Risk of Bias for Systematic Reviews (ROBIS) quality appraisal tool. [3]

SUMMARY OF THE SYSTEMATIC REVIEW

INCLUSION CRITERIA

Any randomised controlled trials (RCTs) comparing cannabinoids for treatment for a range of indications and conditions with usual care, placebo, or no treatment, were eligible for inclusion. The review was commissioned and funded by the Swiss Federal Office of Public Health which pre-specified the eligible indications and conditions (See Table 1).

Table 1: Indications for medicinal cannabis included in the Whiting et al. 2015 review

Included indications and conditions
Nausea and vomiting due to chemotherapy
Spasticity due to multiple sclerosis (MS) or paraplegia
Appetite stimulation in HIV/AIDS
Chronic pain
Depression
Anxiety disorder
Sleep disorder
Psychosis
Glaucoma (reduction in intraocular pressure)
Tourette's syndrome
Any adverse events associated with medicinal cannabis

For this MRC Policy Brief, three researchers from the MRC Alcohol, Tobacco and Other Drug Research Unit independently identified the top five indications to be included in the Brief, based on burden of disease and potential relevance to the South African context. These are:

1. Nausea and vomiting due to chemotherapy
2. Appetite stimulation in HIV/AIDS
3. Chronic pain
4. Spasticity due to MS or paraplegia
5. Glaucoma

METHODS USED IN SEARCHING FOR STUDIES AND ANALYSIS

Two authors searched 28 medical databases from inception to April 2015 to identify eligible trials, independently extract data, and evaluate the risk of bias in each included study. Where possible, results were pooled using random effects meta-analysis. If data could not be pooled, a narrative synthesis was conducted.

RESULTS

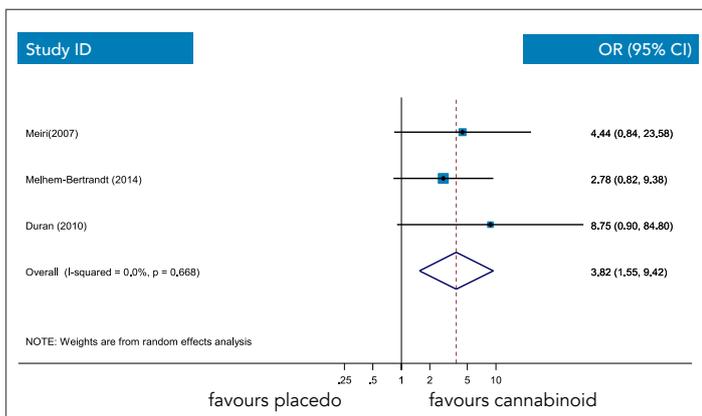
The authors identified 79 eligible RCTs (6462 participants) after screening 23 754 records and assessing 505 full reports.

1. Nausea and vomiting due to chemotherapy

More patients using cannabinoids showed a complete nausea and vomiting response compared to those on placebo (3 RCTs; 47% versus 20%; OR = 3.82 [95% CI: 1.55; 9.42] (See Figure 1).

The quality of evidence was rated as **LOW**.

Figure 1: Number of patients reporting a complete response for nausea and vomiting due to chemotherapy

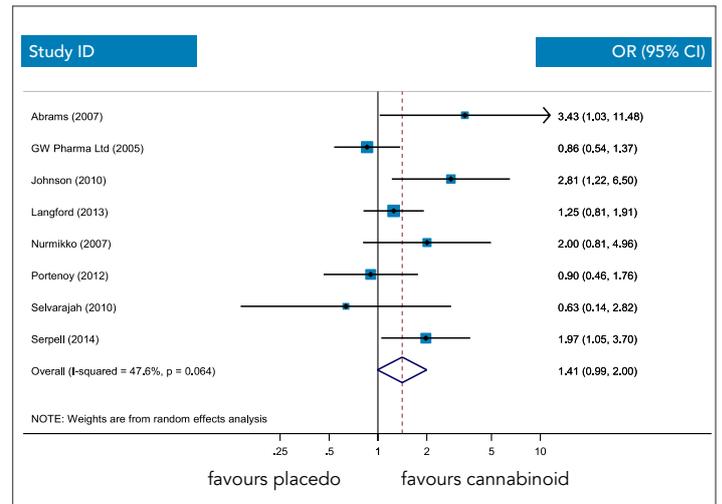


2. Chronic pain

More patients using cannabinoids had reduced pain compared to those on placebo (8 RCTs; 37% versus 31%; OR = 1.41 [95% CI: 0.99; 2.00].

The quality of evidence was rated as **MODERATE**.

Figure 2: Number of patients reporting at least a 30% reduction in pain, data from 8 parallel RCTs



3. Appetite stimulation in HIV/AIDS

Four RCTs reported on the change in weight associated with cannabinoid treatment, but data did not allow for pooling of results. The reviewers report that there was some evidence that dronabinol is associated with weight gain compared to placebo. Evidence for increased appetite, increase in % body fat, and reduction in nausea was more limited and was mostly assessed in single studies.

The quality of evidence was rated as **LOW**.

[Policy Brief Note: All four RCTs predated current antiretroviral therapy and initiation criteria].

4. Spasticity due to Multiple Sclerosis or Paraplegia

The Ashworth scale is a measure of spasticity and assesses spasticity on a scale ranging from 0 (no increase in muscle tone) to 5 (affected part(s) are rigid in flexion and extension).

A negative score indicates an improvement (baseline assessment subtracted from final assessment). Five parallel RCTs provided data which were pooled to indicate that spasticity improved for those participants using cannabinoids compared to placebo (Weighted Mean Difference: -0.12; 95% CI: -0.24, 0.01). (See Figure 3). All participants were suffering from MS.

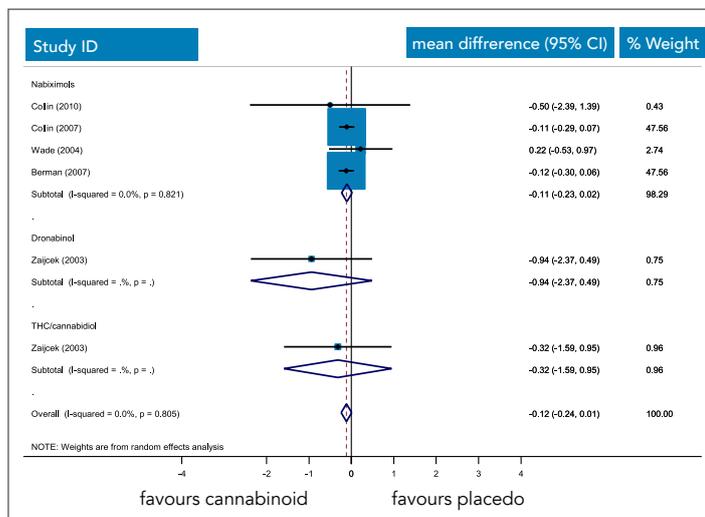
The quality of evidence was rated as **MODERATE**.

[Policy Brief Note: The clinical benefit of this finding is unclear].

ABBREVIATIONS:

- RCT:** Randomised Controlled Trial
- OR:** Odds Ratio
- 95% CI:** 95% Confidence Interval

Figure 3: Weighted mean difference for Ashworth scale for participants with spasticity taking cannabinoids compared to placebo



5. Glaucoma

One cross-over RCT found no difference in intraocular pressures between any of the three treatment arms (5mg THC, 20mg cannabidiol, 40mg cannabidiol).

The quality of evidence was rated as **VERY LOW**.

Adverse Effects

Data about adverse events were reported in 62 of the 79 trials. There was an increase in short-term adverse effects in those using cannabinoids (OR = 3.03; 95% CI: 2.42; 3.80).

Adverse effects included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination. No long-term data were available from the included studies.

ROBIS EVALUATION OF THE SYSTEMATIC REVIEW

Two MRC researchers independently evaluated the Whiting *et al.* 2015 review using the ROBIS tool.

Two areas of potential concern were identified:

1. The search strategy did not include databases from the indigenous medicine field and there was no contact with experts in the field.
2. The review was limited to specific conditions specified by the funders and focused on symptom alleviation rather than cure.

Despite the above concerns, the review was judged to be well-conducted and at **LOW** risk of bias, indicating that the results are robust.

Table 2: Graphical representation of final synthesis of ROBIS assessment of Whiting *et al.* 2015

Review	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	RISK OF BIAS IN THE REVIEW
Whiting <i>et al.</i> 2015	√	√	√	?	LOW

√ This domain was judged to be at low risk of bias

✗ This domain was judged to be at high risk of bias

? There was uncertainty regarding the risk of bias in this domain

WHAT CAN WE LEARN FROM THIS SYSTEMATIC REVIEW?

- Based on the ROBIS evaluation indicating the rigour of the systematic review, we can trust the findings of Whiting *et al.* 2015 [1]. The findings of most relevance to South Africa are:

- * There is evidence of moderate quality to support the use of cannabinoids for the treatment of chronic pain;
- * There is evidence of moderate quality that the use of cannabinoids reduces spasticity in Multiple Sclerosis but the clinical significance of this is unclear;
- * There is low quality evidence suggesting that cannabinoids are associated with improvements in nausea and vomiting due to chemotherapy, and weight gain in HIV infection;
- * There is very low quality evidence that cannabinoids reduce intra-ocular pressure in patients with glaucoma;

* There are safety concerns as reflected in the greater number of short-term adverse events reported in those using cannabinoids, and no long-term data from rigorous studies;

- Current evidence does not provide detailed information regarding the appropriate dosage for medicinal cannabinoids (either organic or synthesized) per indication
- It should be noted that approval of any medication goes beyond effectiveness and safety, and policy-makers will be required to consider supply, regulation, route of administration, and cost-effectiveness, as well as the values and preferences of the broader population.

Permission for reproduction of all figures included in this MRC Policy Brief was received from KSR Ltd and are detailed in the full report of the systematic review [4].

UNDERSTANDING THE METHODS

WHAT IS A SYSTEMATIC REVIEW?

Systematic reviews are generally considered to provide the most reliable form of evidence to guide decision makers. A systematic review conducts comprehensive searches of the medical literature to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question. Researchers conducting systematic reviews use explicit methods aimed at minimizing bias, in order to produce more reliable findings. Systematic reviews may, where appropriate, pool results statistically, known as meta-analysis.

WHAT IS ROBIS?

Systematic flaws or limitations in the design or conduct of a review have the potential to bias results. The new Risk of Bias for Systematic Reviews (ROBIS) tool was developed to assess the risk of bias in reviews [2]. ROBIS comprises three phases: (1) assessment of relevance, (2) identification of concerns with the review process, and (3) judgement of the risk of bias.

Phase 2 covers four domains through which bias may be introduced into a systematic review: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. Phase 3 assesses the overall risk of bias in the interpretation of review findings.

HOW DO WE INTERPRET THE QUALITY EVIDENCE?

In well-conducted systematic reviews, the authors will integrate the limitations of the included studies into the results to arrive at an overall quality of evidence. This can be done using the GRADE approach which combines the results of all included studies with an overall assessment of the quality of the included studies [5].

The following domains are assessed: 1) risk of bias in the included studies, 2) the consistency of results across studies, 3) the directness (applicability) of the results, 4) the precision of the results, and 5) publication bias. We interpret the GRADE quality of evidence ratings in the following way:

HIGH: We are very confident that the true effect lies close to that of the estimate of the effect.

MODERATE: We are moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of effect, but may possibly be substantially different.

LOW: Our confidence in the effect is limited: The true effect may be substantially different from the estimate of the effect.

VERY LOW: We have very little confidence in the effect estimate: the true effects are likely to be substantially different from the estimate of effect.

More information on systematic reviews, GRADE & ROBIS can be obtained from Cochrane South Africa at the MRC by emailing cochrane@mrc.ac.za

This MRC Policy Brief was prepared by Nandi Siegfried, Bronwyn Myers and Charles Parry of the Alcohol, Tobacco and Other Drug Research Unit, www.mrc.ac.za/adarg/contact.htm.

REFERENCES

1. Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A.V., Keurentjes, J.C., Lang, S., Misso, K., Ryder, S., Schmidtkofer, S., Westwood, M., and Kleijnen, J., Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA*, 2015. 313(24): p. 2456-73.
2. Reddy SP, James S, Sewpaul R, Sifunda S, Ellahebokus A, Kamaran NS, Omardien RG. Umthente Uhlaba Usamila – The 3rd South African National Youth Risk Behaviour Survey 2011. Cape Town: South African Medical Research Council, 2013.
3. Whiting, P., Savovic, J., Higgins, J.P., Caldwell, D.M., Reeves, B.C., Shea, B., Davies, P., Kleijnen, J., and Churchill, R., ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*, 2015.
4. Kleijnen Systematic Reviews Ltd. Systematic review of cannabis for medical use. 2014; Available from: <http://www.systematic-reviews.com/>.
5. Guyatt, G., Oxman, A.D., Akl, E.A., Kunz, R., Vist, G., Brozek, J., Norris, S., Falck-Ytter, Y., Glasziou, P., DeBeer, H., Jaeschke, R., Rind, D., Meerpohl, J., Dahm, P., and Schunemann, H.J., GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*, 2011. 64(4): p. 383-94.