# National Essential Medicines List Cost-Effectiveness analysis
# Primary Health Care
# Component: Mental health conditions

**Date**: 22October 2014
**Medication**: Risperidone vs. haloperidol, oral
**Indication:** Schizophrenia

**Background:** During the review of the 2008 Primary Healthcare Standard Treatment Guidelines, comments from external stakeholders recommended that risperidone be considered for the management of psychosis as it had a better safety profile than the current recommendation of haloperidol. In addition, the National Department of Health Contract Circular, HP09-2014SD was awarded and it was noted that there was a price reduction of risperidone (30-40%) compared to the previous HP09-2012SD contract circular.

**Aim:** Costing analysis was performed to compare cost-effectiveness of haloperidol versus risperidone for treatment of schizophrenia at primary level of care, based on available good quality evidence published in the literature.

**Method**: A search of the literature was performed to source evidence comparing safety and efficacy of risperidone to first generation antipsychotics. Utilising statistically significant and clinically appropriate outcomes and the current contract circular prices, the incremental cost effectiveness ratio was calculated. A sensitivity analysis was performed, incorporating the upper and lower limits of the confidence intervals; and an additional cost comparison was performed using expert opinion on dosing to determine the real life experience in local context.Direct costs (medication costs) were only considered for the purpose of this analysis.

**Results:** A meta-analysis, funded by the National Institute of Mental Health (Germany) was quality checked using the PRISMA checklist. Risperidone was shown to be have better overall efficacy than first-generation antipsychotic (FGAs) medicines, −0·13 (−0·22 to −0·05, p=0·002). In addition, NNT for one additional responder was 15 (9–36) for risperidone and relapse was reported to be significantly better than FGAs, RR 0·74 (0·63–0·87), NNT: 11 (7–33). Extrapyramidal side effects (EPSE) associated with risperidone compared to FGAs were less, RR (95% CI): 0·61 (0·52 to 0·72). However, not all patients that experience EPSE would require an anticholinergic. It was assumed that 45.8% of patients on haloperidol and 30.8% of patients on risperidone that developed EPSE would require an anticholinergic, based on 1 year data from a RCT by Crespo-Facorro*et al* (2011).
The daily dose ranges for risperidone and haloperidol determined from the meta-analysis was 4-6 mg and 3-20 mg, respectively.
There is a paucity of evidence supporting orphenadrine dose for neuroleptic induced tardive dyskinesia. However, guidelines provided a daily dose of 150 mg daily.
Discounting rate was not factored into this analysis, as short-term studies were analysed in the meta-analysis (duration of 4 to 108 weeks).
The meta-analysis listed a number of studies on risperidone were industry-sponsored. Excluding these studies reduced risperidone's effect size (overall symptoms) to -0.04 which was not significantly different from FGAs.

**Limitations:**

i. Details of anticholinergic medicines used for EPSE was not described in the meta-analysis; dose and indication for orphenadrine derived from BNF(2013) and SAMF(2012).

**Assumptions:**

ii. Doses used in this study were reflective of doses used for maintenance therapy.
iii. Haloperidol was deemed to represent total class effect of all FGAs in this meta-analysis (comparator drug in 95 studies)
iv. Orphenadrine 150 mg oral, daily considered as safe and effective dose for neuroleptic induced EPSE [Paucity of good quality data; recommendations as per guidelines]

v. Direct costs (medication costs) were considered relevant for the purpose of this analysis.
vi. Patients with EPSE that would require anticholinergic medication was extrapolated from randomised, open label study by Crespo-Facorro *et al* (2011): 1 year data - haloperidol = 45.8% vs risperidone = 30.8%, p < 0.0001.

From a provider perspective, the ICER for the meta-analysis and respective sensitivity analyses (comparing risperidone to haloperidol) were as follows:

**Evidence-based cost analysis:**

| Effect | ICER | Sensitivity analysis (lower limit) | Sensitivity analysis (upper limit) |
|---|---|---|---|
| i. Overall efficacy | R8.64 to R117.63 | R5.40 to R73.52 | R21.60 to R294.07 |
| ii. One additional responder | -R16.20 to -R220.56 | -R9.72 to –R132.33 | -R38.89 to –R529.33 |
| iii. Relapse improved | - R11.88 to –R161.74 | -R7.56 to –R102.93 | -R35.65 to –R485.22 |

As it was noted that higher doses of risperidone (4-8 mg) is used in clinical practice, a further cost analysis was performed by extrapolating the efficacy data to these doses. However, it is important to note that this analysis does not adhere to the principles of evidence-based medicine.

**Extrapolated cost analysis:**

| Effect | ICER | Sensitivity analysis (lower limit) | Sensitivity analysis (upper limit) |
|---|---|---|---|
| i. Overall efficacy | -R4.35 to R101.89 | -R2.72 to R63.68 | -R10.88 to R254.71 |
| ii. One additional responder | R8.16 to –R191.04 | R4.90 to to –R114.62 | R19.59 to –R458.49 |
| iii. Relapse improved | R5.99 to –R140.09 | R3.81 to –R89.15 | R17.96 to –R420.28 |

The meta-analysis showed that risperidone effect size was relatively small (-0.13 in terms of overall symptoms), so an additional costing analysis using the minimum effective dose method was used (Leucht *et al*, 2014). Comparative dose of risperidone: haloperidol was considered to be 2 mg: 5 mg based on the minimum effective dose method.

| Risperidone | vs | Haloperidol |
|---|---|---|
| R 5.13 | | R 6.13 |

## Conclusion:

Different scenarios were analysed to provide modeled cost-effectiveness of risperidone compared to haloperidol for management of psychosis at primary level of care. It is important to note the limitations and assumptions of this model during the decision-making process.

## References:


[1]Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009 Jan 3;373(9657):31-41

[2] Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr Bull. 2014 Mar;40(2):314-26.

[3] SAMF, 10th edition, 2012.

[4] BNF for adults, volume 65, 2013.

[5]Crespo-Facorro B, Pérez-Iglesias R, Mata I, Ramirez-Bonilla M, Martínez-Garcia O, Pardo-Garcia G, Caseiro O, Pelayo-Terán JM, Vázquez-Barquero JL. Effectiveness of haloperidol, risperidone and olanzapine in the treatment of first-episode non-affective psychosis: results of a randomized, flexible-dose, open-label 1-year follow-up comparison. J Psychopharmacol. 2011 Jun;25(6):744-54.

[6] PHC STG, 2008.

[7] Adult Hospital level STG, 2012.

[8] Contract circular HP09-2014SD.

[9] Contract circular HP14-2013PM.