South African National Essential Medicine List
Paediatric Hospital Level Medication Review Process
Component:

MEDICINE MOTIVATION:

1. Executive Summary

Date: July 2021
Medicine (INN): Clonidine, oral
Medicine (ATC): N02CX02
Indication (ICD10 code): *Tic disorders (F95)*
Patient population: Paediatric patients with moderate or severe motor and/or verbal tic disorders who are intolerant of or unresponsive to risperidone.
Prevalence of condition: Prevalence of chronic tic disorders and Tourette's Syndrome ranges from 0.3% - 5% and 0.3%-1% respectively in school-going children[1].
Level of Care: Paediatric Hospital Level
Prescriber Level: Paediatrician
Current standard of Care: risperidone
Efficacy estimates: (preferably NNT): Risperidone and clonidine were shown to be equally effective in intention to treat analysis for the Gaffney et al.[5] trial - Mean reduction in YGTSS at 8 weeks: Risperidone 21%, Clonidine 26%.
Safety estimates: Significant increase in weight in risperidone compared to placebo (SMD = 0.82, CI 0.57 to 1.06, p < 0.001; RR 0.91, CI 0.85 to 0.96, p = 0.002)

2. Name of author(s)/motivator(s)

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3. Author affiliation and conflict of interest details

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4. Introduction/ Background

The Current Paediatric Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) 2017, recommends oral risperidone for tic disorders. Although antipsychotics have been the standard of care and efficacious, they have adverse effects, including extrapyramidal effects, effects on prolactin, metabolic effects, weight gain, elevation of cholesterol, sedation and prolongation of QT interval[2]. Thus, alternative agents have been evaluated for tic disorders[Error! Bookmark not defined.]. Clonidine is used in the management of tic disorders and could have a more benign side effect profile[2]. Attention deficit hyperactivity disorder (ADHD) is the most prevalent comorbid psychiatric disorder complicating tic disorders[3] and there is evidence that clonidine is useful for ADHD symptoms with and without tic disorders[4]. It was thus, considered for inclusion as a second line option for those patients who do not tolerate risperidone well.

5. Purpose/Objective i.e. PICO:

-P *(patient/population): Paediatric patients with moderate or severe motor and/or verbal tic disorders*
-I *(intervention): Clonidine, oral*
-C *(comparator): Risperidone, oral and placebo*
-O *(outcome/s): efficacy and safety of clonidine*

- Measured by standardized rating scales: Yale Global Tic Severity Scale (YGTSS),
- Tourette Syndrome Severity Scale,
- Tourette Syndrome Clinical Global,
- Impression Scale, Global Tic Rating,
- Scale, 2-Minute Tic and Habit Count,
- Tic Symptom Self-Report, and
- Safety

6. Methods:

a. **Data sources** Pubmed, Cochrane and Epistemonikos

b. **Search strategy** (childhood tic disorders [MeSH Terms]) AND (clonidine [MeSH Terms]) – Search 1

Due the potentially limited publications available for clonidine in tic disorders, a wider search was conducted to assess potential long term effects of clonidine and risperidone in children for other disorders. Firstly, a search was conducted for studies that included both risperidone and clonidine (Search 2). The search was conducted in PUBMED and comprised MESH terms for risperidone, clonidine, children, and adverse events. Secondly a wider search was conducted on each agent alone exploring long term side effects (Search 3 & 4). Search 3 was conducted in PUBMED and comprised MESH terms for risperidone, children, long term, and adverse events. Search 4 was conducted in PUBMED and comprised MESH terms for clonidine, children, long term, and adverse events.

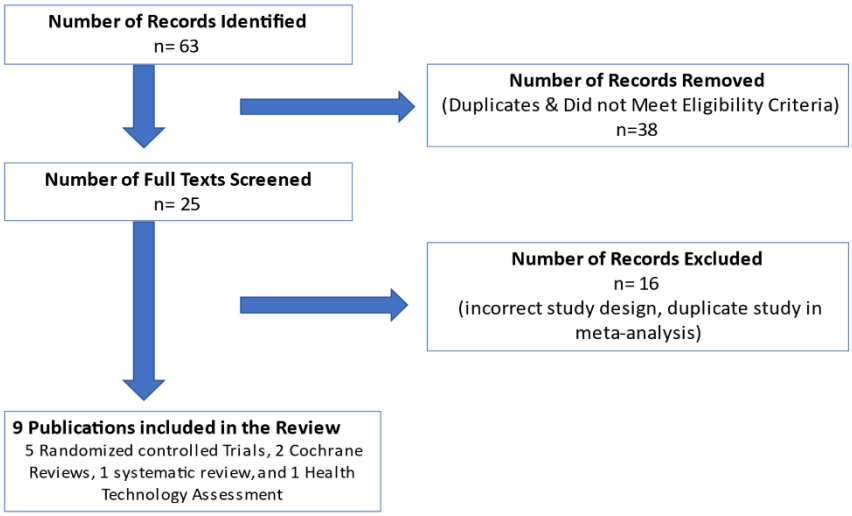
7. Results:

The initial search identified 40 studies (Pubmed - 13 results, Cochrane - 1 result and Epistemonikos - 26 results). After the removal of 9 duplicates, 31 articles were screened. Of these studies, 19 were removed for the following reasons: transcutaneous clonidine use, incorrect design, did not meet eligibility criteria, article retracted. After full-text review 8 articles were excluded due to incorrect comparator, or duplicate study use in meta-analysis. The remaining four studies included two Randomised controlled trials (RCTs), one Cochrane Review and one Health Technology Assessment.

Search 2 produced 29 results and once filters applied to only include systematic reviews, meta-analyses, and RCTS, 4 results remained. Of those two were already included in the initial search and one study focused only on clonidine or risperidone thus were excluded. Search 3 produced 151 results and once filters applied to only include systematic reviews, meta-analyses and RCTS, 8 results remained. Three articles were excluded due to the study design or incorrect comparators resulting in 5 remaining articles. Search 4 produced 59 results and once filters applied to only include systematic reviews, meta-analyses and RCTS, 10 results remained. Of those studies all were deemed not suitable due to incorrect settings or inappropriate study designs.

A total of nine studies were included in the review (*Refer to Figure 1 below*).

Figure 1: Prisma Diagram of Selection of Studies



The findings of the included publications for tic disorders are outlined below in a narrative and summarized in **Table 1: Characteristics of Included Studies for tic disorders.**

8. Description of Findings & Results

Data in Table 1 reports the main characteristics and outcomes of the included studies for tic disorders.

Nine studies were included in this review:

Tic Disorders

(1) A very small, randomized, double-blinded, controlled trial (RCT). The trial included children with Tourette's syndrome aged 7-17 years (n=21). There was a lead in period with placebo followed by 8 weeks of either clonidine or risperidone for 8 weeks[5].

(2) A multicentre, randomized, double-blind clinical trial. A total of 136 children with ADHD and a chronic tic disorder were included. Administered clonidine alone (n=34), methylphenidate alone (n=37), combined clonidine plus methylphenidate (n=33), or placebo (n=32)[3].

(3) A health technology assessment (HTA) exploring different interventions for children with Tourette's Syndrome including pharmacological agents, risperidone and clonidine. The quantitative component included 70 studies. The HTA included the Gaffney *et al*. 2002 RCT[Error! Bookmark not defined.].

(4) A Cochrane review which assessed the effects of pharmacological treatments for ADHD in children with comorbid tic disorders (methylphenidate and clonidine)[6]. The review included the Tourette's Syndrome Study Group RCT[3]. A meta-analysis could not be performed due to heterogeneity of included trials.

Other psychiatric disorders

(5) An 8-week double blind, placebo controlled trial assessing the long-term safety and tolerability of risperidone in children with autism[7] (n=101).

(6) An 8-week double-blind, placebo controlled trial investigating efficacy and safety of risperidone compared to methylphenidate in children with ADHD and oppositional defiant disorders (ODD)[8] (n=-84).

(7) A double-blind maintenance study of 44 weeks following an 8-week double-blind study assessing safety and effectiveness of treatment for early-onset schizophrenia spectrum disorders[9] (n=54).

(8) A Cochrane systematic review examining atypical antipsychotics for disruptive behaviour disorders in children and youths[10].

(9) A systematic review and meta-analysis exploring pharmacological interventions for challenging behaviour in children with intellectual disabilities[11].

COMPARISON 1: Risperidone verses clonidine, oral

Only one RCT comparing clonidine to current standard of care, risperidone[6] (n=21). The Health Technology Assessment[Error! Bookmark not defined.] included the randomized control trial.

- **Mean reduction in Yale Global Tic Severity Scale (YGTSS) -** Risperidone and clonidine shown to be equally effective in treatment of tics[Error! Bookmark not defined.] (Mean reduction in YGTSS: 21% versus 26% respectively). Both treatments significantly efficacious (p = .003)[5] – *low quality evidence.*
- **Adverse events (general) -** No subjects withdrew due to adverse events. Adverse events were clinically significant for both agents (risperidone 33%, clonidine 58% of subjects) however comparison between groups did not reach clinical significance[5, Error! Bookmark not defined.] - *low quality evidence.*
- **Adverse events (sedation) –** Sedation was most common in clonidine group (n=5, 42%)[5]- *low quality evidence*.
- **Adverse events (stiffness)** – Stiffness was most common in risperidone group (n=2, 22%). No evidence of parkinsonism in the two risperidone patients with stiffness was noted[5]- *low quality evidence*.
- **Adverse events (weight change)** - The mean weight change in the risperidone group was +2.1 ± 2.3 kg, versus +0.1 ± 5.9 kg in the clonidine group[5]- *low quality evidence*.

COMPARISON 2: Clonidine, oral versus placebo

One randomized control trial publication (n=136 clonidine n=34)[Error! Bookmark not defined.] and the Health Technology Assessment[Error! Bookmark not defined.] included the RCT[Error! Bookmark not defined.].

- ***Tic severity* –** lessened in all active treatment groups in following order: Clonidine plus methylphenidate, clonidine alone, then methylphenidate alone. For clonidine groups (clonidine and clonidine with methylphenidate) versus non clonidine groups (methylphenidate alone and placebo) tic reduction was significantly improved with the **Yale Global Tic Severity Scale** (**YGTSS)**, 6.2 (1.1, 11.3) p= 0.02. Clonidine versus placebo **YGTSS**, 10.9 (2.1, 19.7) p = 0.003[Error! Bookmark not defined.] - *low quality evidence*.
- **Motor tic score -** favoured clonidine compared with placebo (SMD –0.55, 95% CI–0.90 to –0.20; n = 130). Overall effect z=3.08 (p= 0.002). There was little heterogeneity between studies (I2 = 14%; p = 0.31) [Error! Bookmark not defined.] – *low quality evidence*.
- ***Vocal tic score*** - favoured clonidine but there was no conclusive difference compared with placebo (SMD –0.30, 95% CI –0.62 to 0.01; n = 130). Overall effect: z=1.87 (p= 0.06). There was no heterogeneity between studies (I2 = 0%)[Error! Bookmark not defined.] – *low quality evidence*.
- ***Impairment score*** favoured clonidine compared with placebo (SMD –0.54, 95% CI –0.93 to –0.16; n = 106). Overall effect: z=2.75 (p=0.006). There was no heterogeneity between studies (I2 = 0%)[Error! Bookmark not defined.] – *low quality evidence*.
- ***Global TS*** favoured clonidine compared with placebo (SMD –0.71, 95% CI –1.10 to –0.31; n = 106). Overall effect: z= 3.53 (p=0.0004). There was no heterogeneity between studies (I2 = 0%)[Error! Bookmark not defined.] – *low quality evidence*.
- ***Adverse events (sedation) -*** Moderate to severe sedation experienced more frequently in the clonidine group than placebo (RR 5.65, 95% CI 1.37 to 23.29; n = 40)[Error! Bookmark not defined., Error! Bookmark not defined.] – *low quality evidence*.

COMPARISON 3: Risperidone, oral versus placebo (adverse events only)

- **Adverse events (weight change or excessive appetite)**

- A significant metabolic change was shown (2.8 kg compared with 0kg over 8 weeks, P < 0.001) in one small trial comparing risperidone and placebo (n=34) – moderate quality evidence. Combined with another trial in the HTA analysis for increased appetite/weight gain (Overall effect: z=2.98, p= 0.003; RR 7.68, 95% CI 1.46 to 40.43; n = 80)[Error! Bookmark not defined.] – *low quality evidence*.
- One 8-week trial showed that participants in the risperidone group had significantly higher rates of excessive appetite (p < 0.0001)[7] – *very low quality evidence*.
- A Cochrane Systematic Review evaluating atypical antipsychotics for disruptive behaviour disorders in children and youths found that risperidone was associated with an increase in weight gain of 2.37 kg more than placebo (95% CI 0.26 to 4.49; n=138)[10] – *moderate quality of evidence*.
- Another systematic review (exploring pharmacological interventions for challenging behaviour in children with intellectual disabilities) also reported a significant increase in weight in risperidone compared to placebo (SMD = 0.82, CI 0.57 to 1.06, p < 0.001; RR 0.91, CI 0.85 to 0.96, p = 0.002)[11] – *low quality evidence*.

- **Adverse events (parkinsonism) –** An 8-week study showed that children in the risperidone group had a significantly higher total score for parkinsonism on the Extrapyramidal Symptom Rating Scale (n=48)[Error! Bookmark not defined.] – *low quality evidence*.
- **Adverse events (fatigue/somnolence) –** One 8-week study showed that children in the risperidone group had significantly higher rates of fatigue and somnolence (n-48)[Error! Bookmark not defined.] – low quality evidence. Another 8-week trial also showed significant difference between the risperidone and placebo groups with higher rates of children in the risperidone group experience tiredness during the day (p < 0.0001) and difficulty waking (p < 0.05)[7] – *very low quality evidence*.
- **Adverse events (dizziness or loss of balance) -** An 8-week trial showed significant difference between the risperidone and placebo groups with higher rates of children in the risperidone group experience dizziness or loss of balance (p < 0.05) [7] – *very low quality evidence* .
- **Adverse events (increase in prolactin) –** A systematic review reported that there was significant increase in prolactin found for risperidone compared to placebo (SMD = 3.22, CI 1.68 to 4.75, p < 0.001)[11].

COMPARISON 4: Risperidone, oral compared to other agents (adverse events only)

- Adverse events (weight change)
  - In an 8-week trial there was a significant weight change for participants in the risperidone and placebo group compared to the methylphenidate and placebo group (mean weight change +1.4kg compared to -0.62 kg[8] – *moderate quality evidence*.
  - In a 44-week maintenance study no significant difference in weight was found between groups receiving risperidone, molindone or olanzapine however increase in weight was significant within groups including for risperidone (p < 0.001)[9] – *low quality evidence*.

9. Costing

Table 2: Costing per patient per month

Agent	Regimen	Dose (20kg)	Unit	Tablets p/ day	Price	Strength	Pack size	Price p/ tablet	Source	Cost p/ day	Cost p/ month
Clonidine	starting at 25 mcg and titrate to 3-5mcg/kg	75	mcg	3	R169,33	25	100	R1,69	SEP (Pharmacare)	R5,08	R152,39
Risperidone	starting at 0.25 mg and titrate to average 1mg/day	1	mg	1	R5,29	1	30	R0,18	Contract	R0,18	R5,29

*Single Exit Price: December 21st, 2020 Database, Pharmacare

** Contract price 4 May 2021

Table 3: Sensitivity analysis – cost per patient per month

Agent	SEP	Pack size	40% SEP			60% SEP			80% SEP		
			Price p/pack	Price p/ tablet	Cost p/ month	Price p/pack	Price p/ tablet	Cost p/ month	Price p/pack	Price p/ tablet	Cost p/ month
Clonidine	R169,33*	100	R67,73	R0,68	R60,96	R101,60	R1,02	R91,44	R135,46	R1,35	R121,92

10. Evidence Quality

Overall studies exploring clonidine and risperidone in children with tic disorders are limited. Furthermore, there is a paucity of evidence on adverse effects of risperidone and clonidine in other psychiatry disorders. Majority of studies conducted are of moderate quality but small in size downgrading the strength of the evidence to low quality. Systematic and Cochrane reviews included were of good quality but reiterated the limited evidence available.

11.Discussion

Clonidine and risperidone have been demonstrated, in small studies, to be equally efficacious in the treatment of tic disorders in children. Although evidence is limited and of low quality, adverse events associated with risperidone in particular related to weight gain in children remains a concern. *The Canadian Guidelines for the Evidence-Based Treatment of Tic Disorders: Pharmacotherapy*[2] and the *American Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders* developed by the American Neurology Association both recommend clonidine as first line over risperidone due to the differing side effect profiles[12]. The Canadian guidelines made a strong recommendation based on moderate quality evidence. Although evidence for risperidone was high quality, the recommendation was driven by the consensus with the development group that the side effects experienced with clonidine were preferable to those associated with risperidone. The American guidelines categorised the recommendation for α2 adrenergic agonists such as clonidine in treatment for tic disorders as Level B (should prescribe) and antipsychotics such as risperidone as Level C (may prescribe). The Guidelines cited a number of side-effects associated with antipsychotics that were of concern including weight gain, adverse metabolic side effects and prolactin increase. However, the evidence included in the guidelines had the same limitations in terms of quality (small studies and limited number).

12. Conclusion

There is some evidence to show efficacy of clonidine and risperidone for tic disorders in children and that clonidine may potentially have a more benign side effect profile, however due to the lack of a larger evidence base showing superiority of clonidine and the expected larger cost impact it is recommended that risperidone remain the first line option. However, there is some evidence to show that there are significant side effects associated with risperidone and thus it is proposed that clonidine be considered as an alternative where risperidone is not well tolerated.

Table 1: Characteristics of reviewed studies

i) Meta-analysis/Systematic Reviews/HTAs:

Citation	Study design	Population (n)	Treatment	Outcomes of interest	Effect sizes	Quality appraisal
Osland et.al. 2018[6]	Cochrane Review	Children with ADHD and comorbid tic disorders.	Pharmacological agent for ADHD and comorbid tic disorders, including methylphenidate and clonidine	• Change from base line to week 16 in ADHD Conners ASQ for teachers • Change form baseline in YGTSS	Unable to perform meta-analysis Clonidine verse placebo • See Tourette's Syndrome Study Group	• Low quality evidence for clonidine and methylphenidate.
Hollis et.al. 2016[Error! Bookmark not defined.]	Health Technology assessment; Systematic Review and Qualitative analysis	Children with Tourette Syndrome	Pharmacological, behavioural and physical interventions (including antipsychotic agents and noradrenergic agents)	• Tic reductions primary outcome	Clonidine versus placebo: • Motor tic score favoured clonidine compared to placebo (SMD -0.55, 95% CI -0.90 to -0.20, n=130) • No conclusive difference in terms of vocal tics • Tic-related impairment favoured clonidine versus placebo (SMD -0.54, 95% CI -0.93 to -0.16, n=106). • Adverse effects mild (sedation, dizziness, nausea) Risperidone versus placebo • YGTSS total tic score showed benefit of risperidone versus placebo (SMD -1.10, 95% CI -1.94 to -0.26, n=26) in children specifically, and (SMD -0.62, 95% CI -1.12 to -0.03, n=46) in mixed group. • Overall clinical outcome: More children were improved following risperidone compared to placebo, CGI-Severity score (RR 0.27, 95% CI 0.10 to 0.73, n=26) • Increased rates of fatigue (RR 3.72, 95% CI 1.57 to 8.85, n=80) and increased appetite/weight gain (RR 7.68, 95% CI 1.46 to 40.43, n=80) for risperidone compared to placebo. • No differences in rates of dizziness, depression, increased saliva, tremor, dry mouth or hypertonia. • One study showed weight increase of 2.8kg in risperidone group compared to no change in placebo group (p = 0.001). Risperidone versus clonidine • Child study - Gaffney *et.al*. captured below.	• Mixed adult and child data included. • The quality of trials included is generally low, which downgrades strength of conclusion
Loy et al. 2017[10]	Cochrane Review	Children and youths with disruptive behaviour disorders	Atypical antipsychotics	• Adverse events, effect on weight	• Weight effects favoured placebo, participants in risperidone groups gained 2.37kg more than placebo (95% CI 0.26 to 4.49; n =138)	• Moderate quality evidence found for weight effect

Citation	Study design	Population (n)	Treatment	Outcomes of interest	Effect sizes	Quality appraisal
McQuire et al. 2016[11]	Systematic review	Children with intellectual disabilities and challenging behaviour	Pharmacological interventions	• Adverse events, effect on weight and prolactin	• Review found significant increase in weight in risperidone compared to placebo (SMD = 0.82, CI 0.57 to 1.06, p < 0.001; RR 0.91, CI 0.85 to 0.96, p = 0.002) • Review found that risperidone significantly increases prolactin compared to placebo (SMD = 3.22, CI 1.68 to 4.75, p < 0.001). All studies included in the review showed higher levels of prolactin in risperidone groups compared to placebo however there was significant heterogeneity between ($\chi 2$ = 30.66, p < 0.001, I2 = 93 %).	• Low quality evidence found for weight and prolactin effects.

ii) Randomised controlled studies:

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Quality appraisal
Gaffney et.al. Error! Bookmark not defined.	Randomised, double-blind, controlled trial	Children and adolescents with Tourette's Syndrome	Clonidine *(titrated to a maximum dose of 0.005 mg/kg per day or 0.350 mg/day over 3 to 4 weeks, with a minimum target dose of 0.0025 mg/kg per day)* OR Risperidone *(titrated to a maximum tolerable dose of 0.06 mg/kg per day over 3 to 4 weeks with a minimum target dose of 0.03 mg/kg per day)*	Tic assessment: • Global Severity score (sum of Total Tic score and Tourette's Syndrome Impairment score) from the Yale Global Tic Severity Scale (YGTSS). • Risperidone and clonidine were shown to be equally effective in intention to treat analysis. • Mean reduction in YGTSS at 8 weeks: Risperidone 21%, Clonidine 26% Safety: • Sedation was most commonly reported in clonidine group (clonidine: 42%, n=5; 11%, n=1). • No clinically significant extrapyramidal symptoms observed (Note limitation – short study period). • Stiffness reported in two patients in risperidone group (22%), and 1 patient in clonidine group (8%). • No subjects withdrew due to adverse events. • Comparison between groups in terms of adverse effects did not reach statistical significance.	• Limitations include: natural waxing and waning of symptoms not taken into account. • Study length was only 8 weeks, and may not reflect normal practice. ***Authors Conclusions:*** In this pilot study, risperidone demonstrated efficacy equivalent to clonidine in the treatment of tic symptoms in children and adolescents with TS. Small Sample (n=21) **Selection Bias:** Randomization - **Low Risk** **Performance Bias:** Double blinding - **Low Risk** **Measurement Bias**: Measurement of YGTSS might be subjective – **Moderate Risk** **Attrition bias:** 1 subject in the clonidine group lost to follow-up due to loaf efficacy – **Moderate risk** (8% of clonidine group) **Overall risk of bias: Unclear Risk**
Tourette Syndrome Study Group**Error! Bookmark not defined.**	Multicenter, randomized, double-blind clinical trial.	136 children with ADHD and a chronic tic disorder were included.	Administered clonidine alone (n=34), methylphenidate alone (n=37), combined clonidine plus methylphenidate (n=33), or placebo (n=32).	• Primary outcome was related to outcome of ADHD (ASQ-Teacher). A significant treatment effect was seen in subjects assigned to clonidine (alone or in combination), 3.2 points, 95% CI: 1.2 to 5.2, p = 0.002; versus those not assigned to clonidine (methylphenidate alone or placebo groups). • Secondary outcome of tic severity, lessoned in all active treatment groups in following order: Clonidine plus methylphenidate, clonidine alone, then methylphenidate alone. For clonidine groups (clonidine and clonidine with	• Only included patients with comorbid ADHD and tic disorder. • Study duration of 16 weeks may not mimic normal practice, or be long enough to detect long-term effects. ***Authors Conclusions:*** In this pilot study, risperidone demonstrated efficacy equivalent to clonidine in the treatment of tic symptoms in children and adolescents with TS.

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Quality appraisal
				methylphenidate) versus non clonidine groups (methylphenidate alone and placebo) tic reduction was significantly improved with the YGTSS;6.2 (1.1, 11.3) p= 0.02. Clonidine versus placebo 10.9 (2.1, 19.7) p = 0.003.	Small Sample (n=136) **Selection Bias:** Randomization - **Low Risk** **Performance Bias:** Double blinding - **Low Risk** **Measurement Bias**: Measurement of YGTSS might be subjective – **Moderate Risk** **Attrition bias:** 12% clonidine group versus 22% in the placebo group– **high risk** **Overall risk of bias: Unclear Risk**
Aman et al. 2005[7]	Randomised, placebo-controlled, double-blinded trial	Children with autism	Administered risperidone (n=49) and placebo (n=52)	Adverse Effects: Several side effects were significantly more in the risperidone group: • Tired during the day (p <0.0001), excessive appetite (p < 0.0001), • Difficulty waking (p = 0.05), • Excessive saliva or drooling (p = 0.04), and • Dizziness or loss of balance (p = 0.04). Two events were significantly less common in the risperidone group: • Difficulty falling asleep (p = 0.02) and • Anxiety (p = 0.05).	**Authors Conclusions:** Most AEs were mild to moderate and failed to interfere with therapeutic changes; there were no unanticipated AEs. The side effects of most concern were somnolence and weight gain. Small Sample (n=101) **Selection Bias:** Randomization – **high risk** (randomization had to seize midway) **Performance Bias:** Double blinding - **Low Risk** **Measurement Bias** – **Low Risk** **Attrition bias: 6**% risperidone group versus 33% in the placebo group– **high risk** **Overall risk of bias: High Risk**
Jahangard et al. 2016[8]	Randomised, placebo-controlled, double-blinded trial	Children with ADHD and symptoms of opposite defiant disorder	Administered methylphenidate AND risperidone (n=42) and administered methylphenidate AND placebo (n=42)	Adverse events – weight gain A significant increase in weight was demonstrated in the group with risperidone compared to the group with risperidone (mean weight change +1.4kg compared to -0.62 kg, p < .05).	**Authors Conclusions:** Data suggest that adjuvant RISP improved symptoms in children with ADHD and ODD, but weight gain and higher prolactin levels were also observed, which are two alarming side effects. **Selection Bias:** Randomization - **Low Risk** **Performance Bias:** Double blinding - **Low Risk** **Measurement Bias**:– **Low Risk** **Attrition bias:** No loss to follow-up in either group– **Low Risk** **Overall risk of bias: Low Risk**

Citation	Study design and methods	Population and setting	Intervention and comparison	Main outcomes of interest	Quality appraisal
Findling et al. 2010[9]	Randomised, double-blinded trial	Children and adolescents (8-19 years) with early onset schizophrenia spectrum disorders	Administered molindone (n=20), administered olanzapine (n=13), administered risperidone (n=21)	Adverse events – weight gain A significant increase in weight was found in the risperidone group ($p < 0.001$) compared to baseline but not significantly more compared to the other groups (molindone and olanzapine). Many withdrawals from the trial across groups were due to weight (n=11).	**Authors Conclusions:** No agent demonstrated superior efficacy, and all were associated with side effects, including weight gain Small Sample (n=54) **Selection Bias:** Randomization - **Low Risk** **Performance Bias:** Double blinding - **Low Risk** **Measurement Bias** – **Low Risk** **Attrition bias:** 65% molindone group versus 77% in the olanzapine group versus 81% in the risperidone group. Most of the loss to follow-up was due to adverse events (weight gain 24% in the risperidone group) – **High Risk** **Overall risk of bias: Unclear Risk**

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [ ] Not confident [ ] Uncertain [X]	• The evidence is limited to low quality studies of small number, however, there seems to be consensus in the data of the efficacy of clonidine for tic disorders and that it might have a more benign side effect profile compared to risperidone..
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	• Compared to placebo clonidine is efficacious in the management of tic disorders. • Clonidine and risperidone show similar efficacy for tic disorders. • Clonidine and risperidone have different side effect profiles, and both have shown to be efficacious for tic disorders in children. • The evidence is limited to low quality studies of small number. Clonidine generally appears to be safe, with main adverse event reported usually being sedations. • Risperidone for tics disorder evidence is also limited, however other studies indicate concern of weight gain, which has potential metabolic effects in the future.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. α2-adrenergic agonists - Guanfacine, oral Second generation antipsychotics - Aripiprazole, oral List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:

VALUES & PREFERENCES / ACCEPTABILITY

Is there important uncertainty or variability about how much people value the options?

Minor	Major	Uncertain
		X

Is the option acceptable to key stakeholders?

Yes	No	Uncertain
		X

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
X		

Cost of medicines/ month:

Active Ingredients	Pack Size	Contract Price **	Single Exit Price***	Cost per month (20kg)
Clonidine 25mcg*	100		R169.33	R152.39
Risperidone 1mg	30	R5.29		R5.29

Single Exit Price[xiii]: December 21st, 2020 Database
**Pharmacare*
*** Contract price 4 May 2021*
**** SEP December 2020*

Sensitivity Analysis for Clonidine SEP:

Estimated contract reduction	Cost per month
40%	R60.96
60%	R91.44
80%	R121.92

EQUITY

Would there be an impact on health inequity?

Yes	No	Uncertain
	X	

FEASIBILITY

Is the implementation of this recommendation feasible?

Yes	No	Uncertain
X		

<table>
<tr><td rowspan="2">Type of recommendation</td><td>We recommend against the option and for the alternative</td><td>We suggest not to use the option or to use the</td><td>We suggest using either the option or the alternative</td><td>We suggest using the option</td><td>We recommend the option</td></tr>
<tr><td>☐</td><td>☐</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Recommendation

Rationale:

Level of Evidence:

Review indicator:
Evidence of efficacy: X
Evidence of harm:
Price reduction: X

VEN status:
Vital:
Essential: X
Necessary:</td><td colspan="5">It is suggested that clonidine is utilised as an alternative to risperidone for children with tic disorder when risperidone is not tolerated.

Risperidone and clonidine are shown to be equally efficacious however the side effect profiles differ with clonidine related side effects including sedation for example, as compared to weight gain and metabolic effects in risperidone. However due the large cost difference between the agents and the limited evidence base, it is suggested that risperidone remain first line option for children with tic disorders and clonidine be utilised as an alternative in those patients who are not tolerant to risperidone.

Low quality evidence, small studies</td></tr>
<tr><td>Monitoring and evaluation considerations</td><td colspan="5"></td></tr>
<tr><td>Research priorities</td><td colspan="5"></td></tr>
</table>

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