Hyoscine for clozapine-induced hypersalivation:

a double-blind, randomised, placebo-controlled crossover trial.

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Abstract

Objective: Clozapine is the only evidence-based antipsychotic for treatment-resistant schizophrenia. However, it has considerable side-effects, limiting its usability and reducing patients’ adherence. One of the most common and distressing side-effects is hypersalivation, which can be debilitating, stigmatizing and potentially dangerous through its association with aspiration pneumonia. There is a paucity of evidence guiding possible treatment strategies for hypersalivation. The current study aims to examine the efficacy of hyoscine (scopolamine) for clozapine-induced hypersalivation.

Methods: Fourteen inpatients diagnosed with treatment-resistant schizophrenia, treated with clozapine and suffering from hypersalivation were randomised to receive hyoscine 0.3mg and placebo daily for 4 weeks each in a randomised, double-blind, placebo-controlled crossover trial. The primary outcome was improvement in the Toronto Nocturnal Hypersalivation Scale. Secondary outcomes were change in mass of the pillowcase, anxiety, depression and quality of life.

Results: Hypersalivation significantly improved with hyoscine over placebo when measured by the Toronto Nocturnal Hypersalivation Scale (odds ratio 0.21, 95% CI 0.16–0.28, p<0.001). No significant difference was observed in any of the secondary outcomes.

Conclusion: This study demonstrated a beneficial effect of hyoscine over placebo for clozapine-induced hypersalivation.

Keywords: Schizophrenia, Clozapine, Treatment Resistant, Hyoscine, Scopolamine, Sialorrhea.
Introduction

Clozapine is uniquely effective in treatment resistant schizophrenia, (McEvoy et al., 2006; Siskind et al., 2016) and is the only antipsychotic licensed in the UK for this indication (Mortimer, 2003). However, it is associated with multiple and severe adverse effects which seriously limit its tolerability and disrupt adherence (Yusufi et al., 2007; Taylor et al., 2009; Pai and Vella, 2012). Strategies to manage these adverse effects are in great need, in order to improve quality-of-life.

One of the most common and disabling adverse effects associated with clozapine is hypersalivation, which is more prominent during night-time (Ben-Aryeh et al., 1996; Waserman and Criollo, 2000). The pathophysiology whereby clozapine induces hypersalivation is not clear and several possible mechanisms have been suggested, such as muscarinic M4 receptor antagonism, alpha-2 adrenergic antagonism and oesophageal dysfunction (Zorn et al., 1994; Ben-Aryeh et al., 1996; Praharaj, Arora and Gandotra, 2006).

Several studies have indicated that hypersalivation is one of the most common side-effects of clozapine (>80%) (Hodge and Jespersen, 2008; Maher et al., 2016), could have a substantial effect on the patient’s quality-of-life (Maher et al., 2016), and is an important reason for non-adherence with the treatment (Praharaj, Arora and Gandotra, 2006). Hypersalivation may lead to social embarrassment (Praharaj, Arora and Gandotra, 2006) and speech disturbances and may increase the risk of aspiration pneumonia (Hinkes et al., 1996). However, there is a paucity of clinical trials examining possible treatment strategies to alleviate hypersalivation (Praharaj, Arora and Gandotra, 2006). A Cochrane review of...
the existing studies concluded that the evidence was poor, with lack of clinical data, poor reporting on allocation concealment and randomization, unconfirmed diagnoses, short-term follow-up and inconsistent outcome measures (Syed et al., 2008). Recently, few papers attempting to overcome the evidence gap has been published, examining common yet not-evidence-based treatments, such as Hyoscine [Ref] and Glycopyrrolate [ref].

Hyoscine hydrobromide, known as scopolamine in the United States, is a competitive muscarinic antagonist, and is one of the most commonly prescribed treatments for clozapine-induced hypersalivation in the UK (Kasmi, 2014; Taylor, Paton and Kapur, 2015). It is listed as an unlicensed medication indicated for Clozapine-Induced hypersalivation (CIH) in the British National Formulary (Joint Formulary Committe, 2015). However, there is only one publication of a randomized control trial, which examined the effects of a short-period Hyoscine ointment treatment and yielded negative results, and the evidence supporting its use is based only on published case reports. Therefore, there is an urgent need to address this gap in the evidence base (Chu et al., 2015).

In the current study we have conducted a randomized, double-blind, placebo controlled, crossover trial aimed to assess the efficacy and safety of hyoscine hydrobromide in the treatment of CIH.

**Methods**

**Trial design**
The study was a double-blind, placebo-controlled crossover design. Randomization was equal (1:1).

Participants

Participants were recruited from inpatient psychiatric units at the Bethlem Royal Hospital, a part of the South London and Maudsley NHS Foundation Trust. Patients were eligible to participate in the study if they met the following inclusion criteria:

A. Diagnosis of Schizophrenia or Schizoaffective disorder as per DSM IV-TR criteria.
B. Receiving clozapine for at least two weeks.
C. Clozapine dose in the range 200 – 900 mg per day.
D. A minimum score of 2 on the Toronto Nocturnal Hypersalivation Scale, defined as moderate or worse, on at least 4 occasions within 28 days prior to randomisation.
E. Aged between 18 and 65 years of age.
F. Capable of understanding the information given and giving fully informed consent prior to any study specific procedures.

Patients were excluded if they met any of the following exclusion criteria:

A. Medical conditions that could influence hypersalivation (e.g. idiopathic Parkinson’s Disease).
B. History of an allergic reaction to hyoscine hydrobromide.
C. Any of the following contra-indications to hyoscine as stated in the British National Formulary and electronic Medicines Compendium: Prostatic enlargement, myasthenia gravis, pyloric stenosis, paralytic ileus, glaucoma and pregnancy (see appendix C).
D. A woman of childbearing potential, who has tested negative for pregnancy, or is unable or unwilling to use appropriate contraception during the study.

E. Participation in another therapeutic study within the preceding 12 weeks or use of other investigational drugs or agents.

F. Lack of capacity to provide informed consent to the proposed intervention.

The study was approved by the South-East Research Committee (REC) and was registered at the clinical trials database EudraCT, registration number 2009-016300-23.

**Intervention**

The study began with a 7-day washout period in which no treatment for hypersalivation was given to the participants. This length of the washout was determined according to the half-life of common medications being used to treat hypersalivation. The patients were then randomly assigned to receive either oral hyoscine hydrobromide 0.3mg or placebo. Both the hyoscine tablets and the placebo, comprised of lactose granules, were over-encapsulated, and were identical in mass, taste and appearance. Treatment was administered at 10pm for 28 days. This first period was followed by another 7-days washout, following the patients cross-over to the other arm (e.g. receiving placebo if being administered hyoscine at the first period, and vice versa), for an additional 28 days. Assessments of primary and secondary outcomes were performed in the same manner in both periods. The trial lasted 70 days, from the beginning of the first washout period to the end of the second arm. The study procedure is illustrated in figure 1.

**Primary outcome**
The primary outcome measure was the Toronto Nocturnal Hypersalivation Scale (TNHS), which was developed by combining the Drooling Severity and Frequency Scale (Rashnoo and Daniel, 2015), which rates daytime drooling, with the Nocturnal Hypersalivation Rating Scale (Spivak et al., 1997), which focuses on nocturnal hypersalivation. The TNHS is a 5-point self-rated scale ranging from 0 (no hypersalivation) to 4 (very severe hypersalivation, awakening due to hypersalivation), and has been used in prior studies to measure hypersalivation (Sockalingam, Shammi and Remington, 2009). TNHS scores were recorded daily throughout the study.

**Secondary outcomes**

To obtain an objective measure of the amount of saliva coating the pillow and given criticism that was presented in the literature regarding previous measures (such as diameter of drooling on the pillow), we measured the change in mass of the pillowcase. The patients were given pillows with a waterproof plastic coating, so that any saliva would be absorbed by the pillowcase, and not into the pillow itself. Disposable paper pillowcases were used. Every evening before the patient retired to bed, a new, dry pillowcase was weighed and put on the pillow. The following morning, the pillowcase was removed and weighed between 8-9am. The difference in weight was the outcome measure.

Anxiety and depression were measured using the Hospital Anxiety and Depression score (HADs), which is a 14-item self-rated questionnaire, each item on a scale of 0 to 3 (Zigmond and Snaith, 1983). Quality of life was measured by EuroQol 5-Dimensions questionnaire (EQ-5D), a self-rated questionnaire containing 5 domains (mobility, self-
care, usual activities, pain/discomfort and anxiety/depression), scored on a scale ranging from “I have no problems in [specific domain]” to “I’m unable to [function in that domain]” (Brooks, Rabin and De Charro, 2013). The HADS was recorded once-a-week throughout the study, while the EQ-5D was recorded at the beginning and the end of each period (active/placebo). Adverse Events were logged through all the study phases by the ward clinical team administering the treatment.

**Sample Size**

A power calculation was performed using G*Power 3.0 for Mac OS X. Using repeated measures ANOVA, a sample of 12 participants, each giving 24 measures in each arm would have 80% power to detect an effect size of ≥0.34 (small to moderate) in the primary outcome measure, the TNHS, at the p≤0.05 level, assuming a correlation among repeated measures of 0.3.

**Randomization**

Patients were allocated with serial numbers and equally block-randomized (1:1, blocks of two) by an online randomisation service provided by the Mental Health and Neuroscience Clinical Trials Unit (MH&N CTU) of the Institute of Psychiatry Psychology and Neuroscience at King’s College London. Participants were randomised to receive either hyoscine hydrobromide 0.3mg or placebo, once daily. The randomization service generated emails for the pharmacist, indicating kit number that was then returned to the ward.

**Blinding**
Assignment to either hyoscine or placebo was blinded to the participants, investigators and pharmacy (double-blind). Blinding of the patients and treating physicians and nurses to the allocation status was assured by identical capsules appearance (over-encapsulation) and by identical labelling. Over-encapsulation, packaging and labelling took place at Guy’s and St. Thomas’ Foundation Trust Manufacturing Unit. Blinded packs of study medication were sent to the site pharmacy. Once an eligible in-patient completed the baseline assessment and provided written and informed consent, online randomisation was requested. Emails containing the treatment kit allocation were automatically generated to the requestor, the Chief Investigator, the site pharmacist and the trial manager. A study specific prescription was completed and sent to the site pharmacy for dispensing. The confirmation email was attached to the study prescription, and cross-checked against it, at the point of dispensing.

**Statistical Analysis**

The analyses were pragmatic, based on Intention-To-Treat and utilised all available follow-up data with the trial statistician blind to treatment sequence. The primary outcome variable, TNHS, is ordinal and was analysed using proportional-odds regression. A random intercept for each subject with mean zero and unknown variance to be estimated by the model allowed for within-subject clustering of the repeated measurements. As change over time may be different for different patients, day was also included as a random covariate. The correlation structure of the random effects was assessed using likelihood ratio tests.
As defined, the primary analysis model estimated the mean odds ratio for being in a
different TNHS category in the active arm relative to placebo arm. The treatment
estimate was adjusted for baseline TNHS score, trial period (first or second arm) and day
(within period). Baseline TNHS score adjusts for differences according to baseline
hypersalivation level; the inclusion of period adjusts for potential order effects for
treatment versus control phases and day adjusts for (linear) change in condition within
each treatment period.

Analysis of morning pillow weight used a linear mixed model with the same fixed and
random effect structure but with identity link and normal errors. The HADs analysis used
linear mixed models excluding day as measures were taken once at the end of each
treatment period. Change of EQ-5D scores were assessed using the Wilcoxon matched
pairs-signed rank test. Data management was done in R 2.15 and proportional odds and
regression models were fitted in STATA 14.1 and GLLAMM package (Rabe-hesketh,
Skrondal and Pickles, 2004).

Results

Fifteen patients were screened for eligibility, one of them did not wish to enter the study.
Due to an error, he was randomized, though did not participate in any part of the study.
Thus, the division between the two arms (first-placebo vs. first-treatment) was 8:6, rather
than 7:7. Out of the 14 participants entering the trial, one withdrew during the first arm,
one during the second arm, and one during the second washout period, thus 11
participants completed the trial. The CONSORT diagram is presented in Figure 2. The mean
The age of participants was 38.7 [SD 12.0] years, 29% were female and 43% non-white. The baseline characteristics of the participants are presented in Table 1.

Outcomes

All outcome measures are presented in table 2. Hypersalivation as measured by TNHS ratings (defined as the primary outcome measure) improved significantly: the odds of higher ratings (reflecting greater severity of salivation) were much lower in the period of hyoscine treatment compared to placebo (OR 0.21, 95% CI: 0.16 – 0.28, p < 0.001). The data is illustrated in figure 3. For the secondary outcome measures, there was no difference in the daily pillow-weight measure between the treatment and placebo periods ($X^2(1)=0.00$, $p>0.1$). However, it is important to mention that 50% of the pillow-weight sampling data was missing, mainly due to displacement of the pillowcases and untimely collection of the sample. HADs scores, for both anxiety and depression, did not yield a significant change ($X^2(1)=0.26$, $p>0.1$ and $X^2(1)=0.1$, $p>0.1$, respectively). Finally, EQ-5D showed no difference in quality of life between treatment periods for all the domains and the visual analogue scales (all $p>0.1$).

Adverse events

There were no serious adverse events recorded during the study. Overall there were fewer adverse events recorded in the administration periods relative to the washout, and even fewer differences between the active and the placebo administration Adverse events per organ systems and intervention arm are presented in table 4.

Discussion
This is the first study to examine the common clinical practice of prescribing hyoscine in cases of CIH by a randomized controlled trial. The results show that hyoscine 0.3mg once daily was able to reduce severity of hypersalivation, as reported by the TNHS. None of the secondary outcome measures – mass change of pillowcase, anxiety, depression and quality of life were significantly different between the active and placebo arms. Hyoscine was well tolerated, with rates of adverse events in active treatment similar to rates in the placebo and washout periods. The current study shows that the use of hyoscine 0.3mg once daily is an effective and safe treatment for reduction of clozapine-induced hypersalivation. Hyoscine treatment was not associated with changes in any of the secondary outcomes. The change in weight of the pillowcase did not prove useful and contained high degree of missing data.

**Limitation**

The relatively short follow-up period does not allow us to assess the efficacy and safety of a long-term hyoscine treatment. Though rates and type of adverse events did not differ during the intervention, it should be noted that the small sample size might not have been powered to detect subtler changes. Furthermore, adverse reactions might be more pronounced in a longer-term treatment period, especially due to the anti-cholinergic effect of hyoscine that might aggravate the constipation often reported with clozapine.

The sample size was lower than planned, due to 4 patients revoking their participation or discontinuing the trial. Despite the modest sample size, a significant difference was measured in the main outcome measure, pointing to a substantial effect-size of hyoscine. However, it is possible that this study was under-powered to detect changes in the
secondary outcomes, even more so due to the four patients discontinuing the trial, that led to a smaller sample size than originally planned. It should be noted that while the number of patients was modest, the study used repeated measures analysis, thus including 77 measurement points, which increased the statistical power of this study. Moreover, the cross-over approach allowed us to measure within subject differences between treatment and placebo conditions. Furthermore, the major limitations of cross-over design were addressed by a wash-out period (minimizing the “cross-over” effect) and adjusting for order-effect.

**Generalisability**

Although the sample size was small, patients were from both genders and ethnically diverse. While the study was performed in an inpatient-setting due to the close follow-up needed, it seems that the lack of serious adverse-effect and even lack of increase in side-effects ratio indicates that hyoscine can be administered safely at outpatient clinics as well. It should be noted that the current results contradict those of a previous RCT done with Hyoscine ointment [REF]. It is possible that Hyoscine tablets are more effective than ointment. Additional explaining might stem from the ethnically and genetically different sample as the mentioned study was conducted in Japan. More importantly, the said study did not reveal increased salivation in the Clozapine treated patients, possibly due to relatively low doses of clozapine (mean dose of 136.1), thus the possible effect of hyoscine might not have been evident.
A Cochrane review covering randomized control trials of possible treatment strategies of CIH recommended future studies with clear reporting of randomization and blinding processes, diagnosis, clozapine dosage and treatment duration, with longer follow-up, and a valid and reliable scoring system (Syed et al., 2008). The current study answers most of the scientific gaps noted. All the patients met DSM-IV criteria for schizophrenia or schizoaffective disorder. We used the TNHS, a measure that is equivalent and designed to be more comprehensive than the Nocturnal Hyper-Salivation Rating that had been suggested in prior literature. Furthermore, we attempted to devise an alternative objective measure to nocturnal hypersalivation. The common method in studies published (Syed et al., 2008) was the diameter of the saliva stain in the morning suffers from several drawbacks, such as difficulties to measure asymmetry, type of fabric, mobility of the saliva due to participants’ movements at night. Therefore, we attempted to devise an improved measure using change in weight of the pillowcase overnight. This method was found to have several drawbacks, which might impact its reliability: the effect of room temperature on evaporation; the patients’ sleep duration; the lag between the patients waking up and the ward nurses collection of the pillowcase and the possibility some fraction of the saliva was not soaked in the pillowcase, but rather on the bedsheets, as a result of the patients’ movements at night. Moreover, in our study, a high percentage of the pillowcase-mass data was missing due to technical problems, jeopardizing the validity of any conclusion.

While several studies have noted the importance of hypersalivation as a side-effect and its possible effect on quality-of-life (Waserman and Criollo, 2000), our study did not detect the expected improvement in quality-of-life following the reduction of hypersalivation. It is possible that, while disturbed by hypersalivation, the patients’ quality of life in
inpatients with treatment refractory schizophrenia is dominated by many other prominent factors, such that a change in single side-effect would not be translated into an overall improvement of quality of life.

Conclusions

Hyoscine seems to be an effective and safe method of treatment to CIH, and this study provides evidence to support the common clinical practice of prescribing hyoscine in such an indication. However, the results emphasize the need for additional, longer and larger trials, examining hyoscine and other treatment strategies for CIH – and comparing them to one another in randomized blinded studies. Furthermore, the study suggests the importance of devising better objective methods to quantify hypersalivation.

Acknowledgements

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References


Maher, S. et al. (2016) ‘Clozapine-induced hypersalivation: an estimate of prevalence,


**Figure 1.** Study procedures outline.

- **Recruitment**
- **Blinding and Randomization**
- **Washout for 1 week**
  - Allocated to placebo – 28 days
  - Second washout for 1 week
  - Allocated to hyoscine – 28 days
  - Second washout for 1 week
  - Allocated to hyoscine – 28 days
  - Allocated to placebo – 28 days
- **End of Trial and Analysis**
Figure 2. CONSORT diagram showing the flow of participants through each stage of the trial.

Assessed for eligibility (n=15)

Randomized (n=15)
withdrawn (n=1, randomized in error)

Initial washout for 1 week (n=14)
Complete washout (n=14)

Allocated to placebo – 28 days (n=8)
withdrawn (n=1, unhappy with treatment)
Complete placebo (n=7)

Second washout for 1 week (n=7)
Complete washout (n=7)

Allocated to Intervention – 28 days (n=6)
Complete intervention (n=6)

Allocated to Intervention – 28 days (n=7)
Withdrawn (n=1, unhappy with treatment)
Complete intervention (n=6)

Allocated to placebo – 28 days (n=5)
Complete intervention (n=5)

Included in the analysis (n=14)
Excluded from the analysis (n=1)
Completed the entire study (n=11)
Table 1. Baseline Demographics and clinical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>38.7 (12.0)</td>
</tr>
<tr>
<td>Clozapine dose, mg</td>
<td>322.5 (95)</td>
</tr>
<tr>
<td>TNHS score</td>
<td>2.63 (0.79)</td>
</tr>
<tr>
<td>Increase in mass of pillow, grams</td>
<td>0.79 (1.19)</td>
</tr>
<tr>
<td>HADs Anxiety score</td>
<td>4.6 (2.9)</td>
</tr>
<tr>
<td>HADs Depression score</td>
<td>5.8 (2.4)</td>
</tr>
<tr>
<td>EQ-5D Analogue Scale</td>
<td>78.1 (16.5)</td>
</tr>
</tbody>
</table>

TNHS – Toronto Nocturnal Hypersalivation Scale; HADs – Hospital Anxiety and Depression Scale; EQ-5D - EuroQol 5 dimensions.
Figure 3. Percentage of TNHS ratings by treatment condition
Table 2. Results of all outcome measure in the periods of active treatment and placebo.

<table>
<thead>
<tr>
<th>Treatment (n=10/14)</th>
<th>Placebo (n=12/14)</th>
<th>OR or Adjusted Mean Difference (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean TNHS (SD)</td>
<td>1.6 (1.1)</td>
<td>2.3 (1.1)</td>
</tr>
<tr>
<td>TNHS overall responses (%)</td>
<td></td>
<td>0.21 (0.16, 0.28, p&lt;0.001)</td>
</tr>
<tr>
<td>0</td>
<td>67 (20%)</td>
<td>30 (9%)</td>
</tr>
<tr>
<td>1</td>
<td>107 (31%)</td>
<td>42 (13%)</td>
</tr>
<tr>
<td>2</td>
<td>64 (19%)</td>
<td>73 (22%)</td>
</tr>
<tr>
<td>3</td>
<td>98 (29%)</td>
<td>164 (49%)</td>
</tr>
<tr>
<td>4</td>
<td>2 (1%)</td>
<td>26 (8%)</td>
</tr>
<tr>
<td>Mean pillow weight, grams (SD)</td>
<td>0.66 (0.82)</td>
<td>0.66 (0.83)</td>
</tr>
<tr>
<td>Mean HADs Anxiety (SD)</td>
<td>5.3 (2.7)</td>
<td>5.9 (4.0)</td>
</tr>
<tr>
<td>Mean HADs Depression (SD)</td>
<td>6.2 (3.7)</td>
<td>6.5 (2.0)</td>
</tr>
<tr>
<td>Mean EQ-5D analogue scale (SD)</td>
<td>71.0 (22.6)</td>
<td>67.8 (16.4)</td>
</tr>
<tr>
<td>EQ-5D Mobility problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>8 (80%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Some (%)</td>
<td>2 (20%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>A lot (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EQ-5D Self-care problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>9 (90%)</td>
<td>8 (83%)</td>
</tr>
<tr>
<td>Some (%)</td>
<td>1 (10%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>A lot (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EQ-5D Usual activities problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>5 (50%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Some (%)</td>
<td>5 (50%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>A lot (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EQ-5D Pain/discomfort problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>6 (60%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Some (%)</td>
<td>4 (40%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>A lot (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EQ-5D Anxiety/depression problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>6 (60%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Some (%)</td>
<td>3 (30%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>A lot (%)</td>
<td>1 (10%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

TNHS – Toronto Nocturnal Hypersalivation Scale; HADs – Hospital Anxiety and Depression Scale; EQ-5D - EuroQol 5 dimensions.
Table 4. Adverse Events recorded during the active and placebo periods.

<table>
<thead>
<tr>
<th>Category</th>
<th>Active N</th>
<th>Placebo N</th>
<th>Washouts N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastro-urinary</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurological</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Psychological</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eye, Ear, Nose, Throat</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
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