Taste Evaluation Studies

Piramal Clinical Research
Dr. Sunil Kapur
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• Introduction
• When and How to Introduce Taste/Acceptability Assessment?
• Selection of Human Subjects
• Training of Human Subjects
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• Stimulus Application and Tasting
• Evaluation Principles
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• Pediatric Formulation Taste Assessment Strategy
Piramal Clinical Research

- Full service contract research organization since 2001.
- Approved and audited by regulatory agencies across the globe.
  - USFDA (2009, 2011)
  - WHO (2011)
  - Thailand FDA (2010)
  - MHRA (2003)

- A team of > 60 qualified, experienced and trained professionals.
- All protocols reviewed by IRB registered with OHRP, USA.
- Robust database of approx. 5500 healthy volunteers
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When and How to Introduce Taste/Acceptability Assessment?

Development in adults

- **Preclinical**
  - Exploratory Formulation
  - PIP
  - Ph IIa
  - Ph III
  - Reg

- **Ph I**
  - Paed. Form. Dev.: Assess taste of paed. probe formulations:
    - Adult sensory panels (fully representative?)
    - In vitro methods!!

- **Ph IIb**
  - PK Studies: Include taste assessment in paed. patients to guide PhII/III & commercial DP development

- **Ph III**
  - Results & Compliance

Development in pediatrics

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Selection of Human Subjects*

- 10-24 adult human volunteers will be identified and screened for inclusion and exclusion parameters of the study
  - age,
  - health, subjects with diseases which might affect taste perception such as endocrine disturbances (thyroid gland dysfunction, diabetes mellitus, Cushing’s syndrome), internal diseases (chronic renal failure, cirrhosis of the liver), middle ear affections, xerostomia or depression will not be eligible for the study.
  - use of other medication,
  - consumption of alcohol,
  - pregnancy,
  - smoking behaviour (urine cotinine),
  - H/O of allergic reactions to any ingredient of the test products or artificial sweetner,
  - Impaired stimulation/perception towards taste,
  - dental hygiene.
- Volunteers will be informed about the study procedure, toxicity of drug or formulation and risks involved.
- Informed consent will be obtained on an IRB/IEC approved form.
- Volunteer details (name, age, sex or other information) are kept confidential and will be provided only to IRB/IEC or committees which work in the protection of rights of human subjects.
- Volunteers have to refrain themselves from eating, drinking or chewing gum for at least an hour before testing.

*Exclusive focus on adult taste evaluation in the pilot study
Subsequent evaluation for pediatric taste studies
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Training of Human Subjects

- Human volunteers will be trained to understand the correct way of conducting the taste assessment without considering their personal preferences.
- Training session will include activities like sample application method, tasting of sample, intensity rating, use of appropriate scale and expectoration of samples.
- Volunteers will assess the taste quality, intensity and in some cases temporal profile of samples.
- The correct use of scale will be emphasized to each human volunteer.
- They will receive product specific training before joining a product panel team.
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Study Designs

• Drug exposure is minimized via judicious study design; maximum daily exposure limits are specified in the Protocol and ICF.

• “Sip and spit” tasting protocols are recommended to minimize human exposure to drug actives.

• Designs based on randomisation, blinding, placebo controlled, power calculation, inclusion-exclusion criteria, statistics analysis.

• Standard stimuli
  – Highly pure chemicals or drugs and deionized water will be employed in preparation of standard solutions for stimulus application.
  – Freshly prepared solutions will be utilized for taste assessment but if storage of solution is required they will be kept at 4-8°C in amber glass bottles.
  – Stored solutions will be brought up to room temperature prior to testing with the aid of a water bath.
  – Deionized water will be used as the blank stimulus and the rinsing agent.
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Stimulus Application and Tasting

- Volunteers will rinse and expectorate with deionized water several times prior to testing for neutralization of previous tastes.
- Small (2-5 ml) amount of drug solution or drug or drug in powder or granules or drug product unit dose, standard or test, is dispensed using disposable pipettes or sipped from test tubes or medicine cups or placed on the tongue by scooping.
- Volunteers taste the applied sample by holding it for an appropriate time in the mouth (10-20 seconds), rate taste qualities using visual analogue scale (VAS) and then rinse mouth thoroughly with deionized water after each tasting.
- The rating for overall liking may be repeated after 2-5 minutes upto 2 hours (as per the protocol).
- Salty crackers and water will be provided to neutralize taste after tasting standard or test sample.
- Taste evaluation for next sample starts only after proper neutralization of taste due to previous stimulus.
- Subjects will wear nose-clips to eliminate olfactory input while rating.
- For estimation of bitterness intensity standard solutions of quinine hydrochloride, caffeine may be used.
- ± Bioequivalence study arm may be added based on sponsor’s requirement.
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Evaluation Principles

• Evaluate parameters like taste, aftertaste, flavor, aroma, texture and mouthfeel.
• Questions for asking the individual perception for the adjectives will be kept simple, and intelligible.
• Asked questions will as much as possible be independent of the age, social and developmental level of the volunteers.
• Simple language and commonly used terms relevant to the age of volunteer will be used to describe the properties of taste characteristics, aftertaste, flavor, texture and mouthfeel.
  – Taste Characteristics: sweet, salty, sour, and bitter.
  – Aftertaste: Bitter, sweet, salty, sour, umami, astringent, numbness, or freshness.
  – Flavor and aroma.
  – Texture and mouthfeel: thin, thick, viscous, gritty.
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Analysis

- **Affective testing (Subjective)**
  - Hedonics
  - Just-about-right
  - Preference

- **Effective/analytical testing**
  - Objective/facts = discrimination tests
  - Difference testing (triangle, duo-trio, paired and multiple comparisons)

- Descriptive analysis
- Ranking
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Elements of Regulatory Support

- Piramal HealthCare Corporate Regulatory
- Piramal Clinical Research QA/Regulatory (8)
- Piramal Clinical Research Dedicated Liaison Personnel (1)
- Piramal Healthcare Liaison Office (Delhi)
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Scenario 1

- Formulation: generics (export)
- Large amount of safety data/record available
- IRB approval required
- Regulatory risk: Very minimal
- Regulatory complexity: Less than a typical BA/BE study
- Turnaround time: 6-8 weeks (6 weeks target)
- Major Documents required:
  - Study protocol
  - ICF
  - Sponsor's authorization
  - Justification for conducting the study
  - Stability data (minimum 1 month)
  - CoA
  - SOP for volunteer recruitment
  - IEC composition
- Piramal Clinical Research (PCR) regulatory will play an active role through liaison office (Delhi)
- Minimal involvement of Piramal Healthcare (PHL) corporate regulatory anticipated
  - Support role
  - Advisory role
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Scenario 1 (roles/responsibility)

- **DCGI**
- **Dedicated Liaison**
- **PHL Corporate Regulatory**
  - Keep in the loop
  - Advisory/Support
- **PCR Regulatory & QA & Operations**
  - *Active Role* on need basis only
  - Keep in the loop
- **PCR Head**
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Scenario 2

- Formulation: NCE
- No safety data/record available
- IRB approval required
- Regulatory risk: Higher than scenario 1
- Regulatory complexity: More than a typical BA/BE study
- Turn around time: 12 to 16 weeks (target 14 weeks)
- Major Documents in addition to scenario 1:
  - Safety data
  - Toxicity data
- Piramal Healthcare corporate regulatory will play an active role (as applicable)
  - E.g. Safety/Toxicity data issues
  - Response to major queries
- Piramal Clinical Research Regulatory will provide full supportive role to Piramal Healthcare corporate regulatory
  - Will be responsible for dossier compilation and submission
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Scenario 2 (roles/responsibility)

**PHL Corporate Regulatory**

- Active support

**PCR Regulatory & QA & Operations**

- *Active Role in regulatory dossier submission*
- **Active role anticipated (as applicable) e.g. response to major safety/toxicity queries**

**PCR Head**

- DCGI
- Dedicated Liaison
- Response to major safety/toxicity queries
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Clinical Taste Evaluation Panel/Timelines

- Set-up of a taste panel (including selection and training of human volunteers) = 1-2 months / one time cost

- Study-specific
  i. Development of study protocol*: 3 weeks
  ii. IRB approval: 2 weeks (not critical path)
  iii. Regulatory (DCGI) approval: 8-14 weeks (parallel to ‘ii’ above)
  iv. Taste assessment study (n=10-24): 1-2 week
  v. Placebo and various add-ons will be provided#
  vi. Panel will pick top two choices#
  vii. Client will select one/two for formulation development#

*Standard Template procurement under process
# Study/Client specific
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Taste Evaluation in Pediatric Formulations is Critical

- Survey of over 800 paediatricians on barriers to treatment completion for children with acute/chronic illnesses: (American Society of Pediatrics; 2000)
- Frequency of dosing (96%/91%)
  - Unpleasant taste (91%/84%)
  - Side effects of medication (88%/88%)
- Compliance rates in children range from 11-93%, with major factors attributed to formulation and palatability (Matsui. 2007. PPDT 8: 55-60)
Pediatric Formulations

Clinical taste evaluation approach

• In case of NCE in advanced stage (Phase II/III), conducting studies in India will not be an regulatory issue. Phase I will be a regulatory challenge

• Studies can be conducted for pediatric formulations but these will be done in adults. Swirl and spit approach will be used, unless necessary to swallow

• Panel selected based on “closeness” to pediatric perception; established via evaluation of common food items’ taste and perception

• Parameters evaluated (not limited to) Taste, Aftertaste, Flavor, Aroma, Texture and Mouthfeel
Change in Ability to Cope with Dosage Forms

ICH E11

Preterm newborn infants → Term newborn infants → Infants and toddlers → Children → Adolescents

0 → 1 month → 2 years → 6 years → 12 years → 16 years → 18 years

Preterm newborn infants → Term newborn infants → Infants and toddlers

Preschool children → School children

Can’t → could? → (small) Can swallow Tablets/Capsules

Acceptable Tablet size?
Nothing on capsules

3-5mm >2yo
5-10mm >6yo
10-15mm >12yo
15mm+ >18yo

catherine tuleu 2011

Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use
19 May 2011 EMA/CHMP/QWP/180157/2011
Pediatric Formulations
Work Flow Algorithm & Role of Piramal Clinical Research

PreForm

Dev

Clin Mfg

Clin. Panel

Commercial Manufacture

Liquid/ Solids
Mumbai

Solution/ Suspension
Mumbai

Powder for soln/susp
Ahmedabad

Tablet Form
Ahmedabad

Solution/ Suspension
Sponsor’s site / Our future site

Powder for soln/susp
Ahmedabad

Tablet Form
Ahmedabad

Taste Human Evaluation
Hyderabad

Solution/ Suspension
Sponsor’s site / Our future site

Powder for soln/susp
Sponsor’s / Our future site

Tablet Form
Ahmedabad / Pithampur / UK
THANKS
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<tbody>
<tr>
<td>Suppression of bitterness by sodium.</td>
<td>Subjects Number: 12-27; Age 21 to 36</td>
<td>Standard solutions prepared in de-ionized water: Urea, caffeine, quinine HCl, amiloride were used as bitterness standards</td>
<td>Bitter salt mixture series (containing only one salt and one bitter agent), each solution (n=12 or n=16) was sampled twice</td>
<td>All samples were delivered in 10 ml volumes in polystyrene medicine cups</td>
<td>After tasting subjects were required to rinse twice thoroughly with deionized water during the approximate 60 s interstimulus interval.</td>
<td>Intensity matching method was adopted with 0.1 and 1.0 mM QHCl as medium and high levels of bitter sensation</td>
<td>Breslin and Beauchamp, 1995</td>
</tr>
<tr>
<td>Selective inhibition of bitterness by phospholipids.</td>
<td>5 to 8 paid volunteers</td>
<td>Standard quinine sulfate, sucrose, sodium chloride, tartaric acid known concentrations for values on intensity scale from 1 to 10</td>
<td>Solutions of sucrose, sodium chloride, tartaric acid, quinine sulfate with added phospholipids (Phosphatidic acid, phosphatidylethanolamine, phosphatidylinositol, phosphatidylcholine) and granules quinine + phospholipids granules</td>
<td>Test and standard solutions: About 5 ml of each solution was added to a separate test tube placed on the tongue. Granules: 100 mg were placed on the tongue till granules were completely dissolved on the tongue</td>
<td>Rinsing of mouth thoroughly with deionized water</td>
<td>10 point bitterness intensity scale</td>
<td>Katsuragi et al, 1997</td>
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<tr>
<td>Inhibition of bitter taste of Polymyxin B Sulfate and Trimethoprim Sulfamethoxazole by BMI-60.</td>
<td>Children in age group 3 to 6 = 5; Children in Age Group 8 to 15 = 4; Total nine children. Adult Volunteers: Five</td>
<td>Quinine sulfate solution at different bitterness intensities (1 to 10)</td>
<td>Dissolving one polymyxin B sulfate, one bacitracin (sulfamethoxazole + trimethoprim) tablet and one polymyxin B sulfate plus one bacitracin tablet in 10 ml of deionized water. Effect of addition of BMI 60 from 0.05 to 1 g was evaluated</td>
<td>Teaspoonful of solution placed on the tongue</td>
<td>Rinsing of mouth thoroughly with deionized water</td>
<td>10 point bitterness intensity scale</td>
<td>Saito et al, 1999</td>
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* Not a comprehensive list
### Key Literature (Taste Assessments Trials)

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<tr>
<td>Palatability and cost comparison of five liquid corticosteroid formulations</td>
<td>Double blind palatability test (taste, aftertaste, texture and overall acceptability) of five liquid corticosteroid formulations</td>
<td>No standard bitterness solution. Only five test formulations were used.</td>
<td>Taste masked commercial formulations Pedipred, Prelone, prednisone oral solution and prednisone 10-mg tablet crushed in 10 ml of cherry syrup</td>
<td>A few drops of formulation was placed on the spoon and administered at home by the family members to patients</td>
<td>Five point scale (least palatable to most palatable). Subjective responses like significant facial expressions, comments, behavior etc.</td>
<td>Hutto et al, 1999</td>
<td></td>
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<tr>
<td>Taste masking as a consequence of organi-</td>
<td>A single blind taste test was used for the taste-masking evaluation. A panel of 10 healthy volunteers: six females and four males with ages ranging from 18 to 40 and weights ranging from 47 to 80 kg participated in this study and gave their informed consent.</td>
<td>Pure excipient and pure active ingredient was also given apart from drug excipient mixtures. Powders were placed on microscope slides. The volunteers were asked to taste the powders by sampling them directly with their tongue.</td>
<td>Binary mixtures of drug with excipients (niflumic acid, Ibuprofen; Excipient, ethylcellulose, HPMC, with</td>
<td>each volunteer tasted five powders at least 2 h after lunch or coffee for 4 days</td>
<td>Five powders were tasted 2 hr after lunch or coffee for four days</td>
<td>Barra et al, 1999</td>
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<td>Palatability of oral antibiotics effective in the therapy of otitis media in healthy pediatric volunteers</td>
<td>Single-blind, multicenter, randomized, comparative taste test for 4 antimicrobial suspensions was conducted at 3 primary care pediatric centers and involved a volunteer sample of 90 healthy children (5 to 9 years of age).</td>
<td>Only test samples of 2.5 ml each antimicrobial suspension was given to patients.</td>
<td>Azithromycin (cherry flavored), cefprozil (bubble gum flavored), cefixime (strawberry flavored), and amoxicillin/clavulanate (banana flavored).</td>
<td>The antimicrobial agents were presented in a balanced, randomized order as determined by arrangement in a Latin square.</td>
<td>Cracker to eat and rinse and swallow water.</td>
<td>10-cm VAS visual analog scale (VAS).</td>
<td>Toscani et al, 2000</td>
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<tr>
<td>A taste study of several antibiotic suspensions</td>
<td>This randomized, single-blind, paired-comparison crossover study</td>
<td>Amoxicillin antibiotic suspension was used as positive.</td>
<td>Cefuroxime axetil suspension (125 mg/5 ml or 250 mg/5 ml) with that of 3 other antibiotic.</td>
<td>They were then administered in counterbalanced order 2.5 ml of 2.</td>
<td>2-3 minute washout period; palate cleansing with soda cracker and water.</td>
<td>5-point facial hedonic scale (from 1 = really bad to 5 = really good).</td>
<td>Schwartz et al, 2000</td>
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<td>Taste Test: Children rate flavoring agents used with activated charcoal</td>
<td>Double blind study randomized Healthy volunteers age 3 and 17 in prospective masked trial; Subject tasted 5 substances in random order</td>
<td>Activated charcoal without and with coca cola, cherry flavored syrup, chocolate milk and sorbitol</td>
<td>5 ml of test samples were sipped once</td>
<td>water in between more samples</td>
<td>Less than 8 year used 10 point facial hedonic scale; Over 8 years used 100 point visual analog scale</td>
<td>Skokan et al, 2001</td>
<td></td>
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<td>Sensory evaluation of albendazole suspensions</td>
<td>n=24 trained judges in individual cabins; Sensory analysis repeated twice in completely randomized blocks. Blinding control</td>
<td>Three formulations of albendazole suspension</td>
<td>Holding the sample for till complete impregnation of mouth and the time necessary to detect the difference</td>
<td>Residual taste removed by rinsing with water eating a piece of apple before testing the following sample.</td>
<td>10 point scale (0 to 9) from no difference to extremely different</td>
<td>Frigonezi-Nery, 2002</td>
<td></td>
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<tr>
<td>A taste comparison of three liquid steroid preparations: prednisone, prednisolone and dexamethasone</td>
<td>18 to 50 yr old volunteer; 85 adult volunteer 53 male and 33 female</td>
<td>Commercial steroid preparations of Prednisone prednisolone sodium and dexamethasone</td>
<td>5 ml of steroid preparation; medication cups</td>
<td>saltine cracker and water</td>
<td>Five point scale</td>
<td>Mitchel et al, 2003</td>
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<td>Effect of quinine solutions on intracellular Ca++ levels in neuro 2a cells. Combination effect of L-arginine and NaCl on bitterness suppression of amino acid solutions</td>
<td>Healthy volunteers (nine women and men aged 20-23 years) were well informed and then joined the gustatory sensation tests</td>
<td>The volunteers were first asked to keep standard quinine hydrochloride solutions (0.01, 0.03, 0.1, 0.3, 1.3 mmol/l)</td>
<td>Quinine solutions of various concentrations</td>
<td>In volunteers mouths for 15 s standard and test samples</td>
<td>Gargle with water and 20 minute interstimulus interval</td>
<td>Equivalent density determination method</td>
<td>Nakamura et al, 2003</td>
</tr>
<tr>
<td>Palatability of oral antibiotics among children in an urban primary care centre</td>
<td>30 Healthy children (5-8 years), Randomized single blind taste test to determine palatability of four antimicrobial agents</td>
<td>Only test solutions of antimicrobial suspensions were used in the study.</td>
<td>Azithromycin (cherry flavored), cefprozil (bubble gum flavored), cefixime (strawberry flavored), and amoxicillin/clavulanate (banana flavored).</td>
<td>2.5 ml of the antimicrobial suspension was given in plastic medication cups by research nurse or principal investigator</td>
<td>Cracker to eat and rinse mouth with water and swallow to remove residual taste</td>
<td>10 cm VAS incorporating a facial hedonic scale</td>
<td>Angelli et al, 2004</td>
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<td>The combination effect of L-arginine and NaCl on bitterness suppression of amino acid solutions</td>
<td>Six adult volunteers</td>
<td>Standard Quinine hydrochloride concentrations 0.01, 0.03, 0.10, 0.30 with corresponding bitterness scores 0, 1, 2, 3, and 4, respectively.</td>
<td>Test chemicals were sweeteners (sucrose, aspartame), NaCl, various acidic (L-aspartic acid, L-glutamic acid), or basic (L-histidine, L-lysine and L-arginine) amino acids, tannic acid and phosphatidic acid</td>
<td>Scooping 2-5 ml of standard or test solution on the tongue and granules on the tongue. All samples were kept in the mouth for 15 s.</td>
<td>Rinsing of mouth thoroughly with deionized water and interstimulus interval of 20 minutes.</td>
<td>Intensity scale 1 to 4 (Equivalent density examination method)</td>
<td>Ogawa et al, 2004</td>
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* Not a comprehensive list
### Key Literature (Taste Assessments Trials)

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<th>Study</th>
<th>Subjects and Study Plan</th>
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<td>Evaluation of bitterness intensity of commercial taste masked clarithromycin dry syrup (Taginake et al, 2003) Evaluate the bitterness of 18 different antibiotic and antiviral formulations for pediatrics (Ishizaka et al, 2004); Bitterness suppression of macrolide dry syrups by jellies (Tsuji et al, 2006)</td>
<td>5 to 9 healthy adult volunteers, n=9 (Taginake et al, 2003), n=7 (Ishizaka et al, 2004)) n= 5 or 6 (Tsuji et al, 2006)</td>
<td>Standard Quinine hydrochloride concentrations 0.01, 0.03, 0.10, 0.30 with corresponding bitterness scores 0, 1, 2, 3, and 4, respectively.</td>
<td>Taste masked formulations</td>
<td>Scooping 2-5 ml of standard or test solution on the tongue and granules on the tongue. All samples were kept in the mouth for 15 s.</td>
<td>Rinsing of mouth thoroughly with deionized water and interstimulus interval of 20 minutes</td>
<td>Intensity scale 1 to 4 (Equivalent density examination method)</td>
<td>Taginake et al, 2003; Ishizaka, 2004; Tsuji et al, 2006</td>
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<td>Rapidly disintegrating risperidone summary of phase 1 clinical trials assessing taste, table disintegrating time, bioequivalence and tolerability</td>
<td>Four open label, Randomized Crossover trials; 1 was pilot trials, and all of the trials were short-term. Age of subjects 18 to 65 years and physically healthy (volunteers) or had a diagnosis of schizophrenia of any subtype or schizoaffective disorder.</td>
<td>Rapidly disintegrating and conventional risperidone tab lets.</td>
<td>RDT placed on tongue till it disintegrates completely and held in the mouth for appropriate time to assess the taste.</td>
<td>Coffee, tea, soft drink, a piece of cake after administration of RDT</td>
<td>5-step scale (1 = &quot;very nice/pleasant&quot;; 2 = &quot;nice/pleasant&quot;; 3 = &quot;neutral&quot;; 4 = &quot;bad&quot;; and 5 = &quot;very bad&quot;) for measuring intensity of taste.</td>
<td>Thyssen et al, 2007</td>
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