CYPROHEPTADINE: A POTENTIALLY EFFECTIVE TREATMENT FOR FUNCTIONAL GASTROINTESTINAL DISORDERS IN CHILDREN

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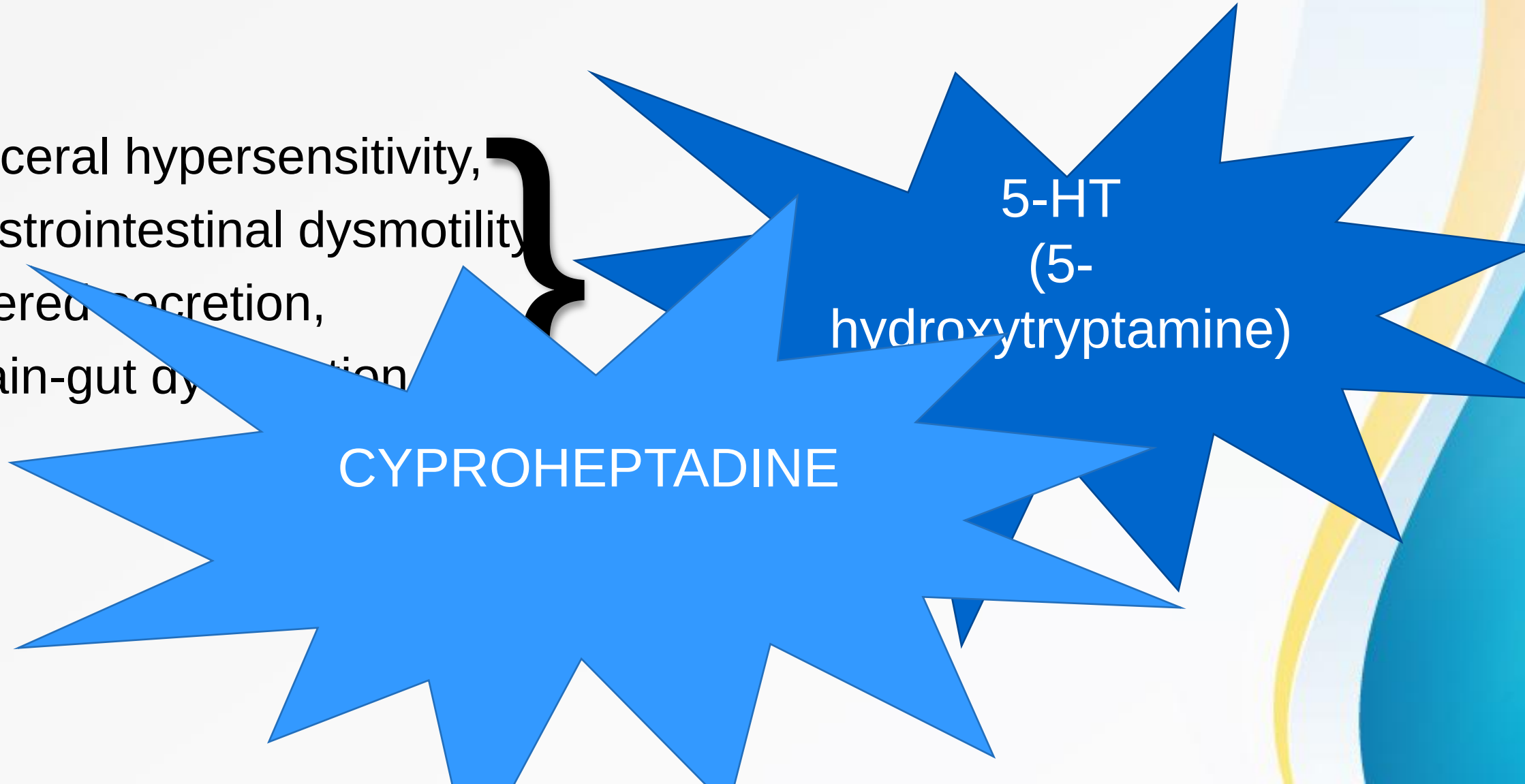
WHAT IS FGIDs?

- Persistent and recurring GI symptoms
- Not caused by structural or biochemical abnormalities
- FGIDs contain:
  - Functional abdominal pain (FAP)
  - Functional dyspepsia (FD)
  - Irritable bowel syndrome (IBS)
  - Abdominal migraine (AM)
  - Cyclic vomiting syndrome (CVS)

Pathophysiology

- Visceral hypersensitivity,
- Gastrointestinal dysmotility
- Altered secretion,
- Brain-gut dy tion



CYPROHEPTADINE IN FD

Author	Participants	Study criteria		Intervention	Outcome measures	Result	Side effect
		Inclusion	Exclusion				
Madani et al.	Children age 1-18y (N=34 for FD) Retrospective review	Rome III-defined FGIDs 1-75 mo follow up	Cyp not used or used for other causes, no follow-up visit	Mean initial dose 0.14mg/kg/day Mean final dose 0.14mg/kg/day in CIG, 0.2mg/kg/day in NIG/PIG Median duration:6mo (range,1-48 mo)	Grade responses	Complete improvement in FD 77% (26 of 34)	27% in CIG 46% in NIG/PIG 46% in NIG/PIG Somnolence 12% Weight gain 10% Other 6% Combination 3% Increased appetite 1%
Rodriguez et al.	Children age 3-15y (N=12) Retrospective review	Dyspepsia organic cause or FD (Rome IIIrefractory to convential treatment, given Cyp	Cyp given solely as an appetite stimulant	Median dose 0.19 mg/kg/day (range 0.04-0.62 mg/kg/day) Median duration: 20 wk (range, 2-222wk)	Grade responses	Significant response 41%, resolved 14%, failed 45%	Side effect 30% Somnolence 16% Behavioral change 6% Weight gain 5% Abdominal pain 2.5%

CYPROHEPTADINE IN FAP

Author	Participants	Study criteria		Intervention	Outcome measures	Result	Side effect
		Inclusion	Exclusion				
Madani et al.	Children age 1-18y (N=55 for FAD) Retrospective review	Rome III-defined FGIDs 1-75 mo follow up	Cyp not used or used for other causes, no follow-up visit	Mean initial dose 0.14mg/kg/day Mean final dose 0.14mg/kg/day in CIG, 0.2mg/kg/day in NIG/PIG Median duration:6mo (range,1-48 mo)	Grade responses	Complete improvement in FADP 66% (36 of 55)	27% in CIG 46% in NIG/PIG 46% in NIG/PIG Somnolence 12% Weight gain 10% Other 6% Combination 3% Increased appetite 1%
Sadeghian et al.	Children age 4.5-16y (N=29) Double-blinded, randomized, placebo-controlled trial	FAD (Rome III)	Other diseases, FAD with atypical features, abdominal ECG, abdominal migraine, chronic pain, RUQ/RLQ, pain relieved by lactose-free diet	Dose 0.25-0.5 mg/kg/day (maximum 12mg/day children 2-6y, maximum 16mg/day children 7-14y) Median duration: 2wk	Self-reported scales: Frequency and intensity of abdominal pain Children's and parent's impression	Improved/ resolved pain frequency (p=0.002) with RR 2.43 (95%CI, 1.17-5.04), Decreased pain intensity (p=0.001) with RR 3.03(95%CI, 1.29-7.11) Children's/Parents' impression in Cyp group (87% vs 36%; p=0.005)	Increased appetite3% Hypoactive airway 3% No serious side affects reported

CYPROHEPTADINE IN AM

Author	Participants	Study criteria		Intervention	Outcome measures	Result	Side effect
		Inclusion	Exclusion				
Madani et al.	Children age 1-18y (N=18 for AM) Retrospective review	Rome III-defined FGIDs 1-75 mo follow up	Cyp not used or used for other causes, no follow-up visit	Mean initial dose 0.14mg/kg/day Mean final dose 0.14mg/kg/day in CIG, 0.2mg/kg/day in NIG/PIG Median duration:6mo (range,1-48 mo)	Grade responses	Complete improvement in AM 72% (13 of 18)	27% in CIG 46% in NIG/PIG 46% in NIG/PIG Somnolence 12% Weight gain 10% Other 6% Combination 3% Increased appetite 1%
Worawattanakul et al.	Children age 3-15y (N=12) Retrospective review	AM treated with medication	Follow-up data could not be obtained	Dose 0.25-0.5 mg/kg/day Median duration: 2-36mo	Grade response: exellent, fair, poor	12 patients treated with Cyp: Exellent 33% Fair 50% Poor 17%	Drowsiness 8% Weight gain 8%
Pfau et al.	Children age 3-15y (N=106;n=19 by Lundberg's criteria) Retrospective review	Undiagnosed recurrent vomiting	Previously diagnosed with other diseases	4 of19 patients with AM received Cyp Unknown dose and duration	Grade response: complete resolution, some response, or no response	Complete resolution 75% (3 of 4 patients)	No report

CYPROHEPTADINE IN IBS

- No study demonstrating a direct effect of Cyp

Author	Participants	Study criteria		Intervention	Outcome measures	Result	Side effect
		Inclusion	Exclusion				
Madani et al.	Children age 1-18y (N=10 for IBS) Retrospective review	Rome III-defined FGIDs 1-75 mo follow up	Cyp not used or used for other causes, no follow-up visit	Mean initial dose 0.14mg/kg/day Mean final dose 0.14mg/kg/day in CIG, 0.2mg/kg/day in NIG/PIG Median duration:6mo (range,1-48 mo)	Grade responses	Complete improvement in IBS 100% (10 of 10)	27% in CIG 46% in NIG/PIG 46% in NIG/PIG Somnolence 12% Weight gain 10% Other 6% Combination 3% Increased appetite 1%

CYPROHEPTADINE IN CVS

Author	Participants	Study criteria		Intervention	Outcome measures	Result	Side effect
		Inclusion	Exclusion				
Madani et al.	Children age 1-18y (N=8 for CVS) Retrospective review	Rome III- defined FGIDs 1-75 mo follow up	Cyp not used or used for other causes, no follow-up visit	Mean initial dose 0.14mg/kg/day Mean final dose 0.14mg/kg/day in CIG, 0.2mg/kg/day in NIG/PIG Median duration:6mo (range,1-48 mo)	Grade responses	Complete improvement in CVS 75% (6 of 8)	27% in CIG 46% in NIG/PIG 46% in NIG/PIG Somnolence 12% Weight gain 10% Other 6% Combination 3% Increased appetite 1%
Li et al.	Children younger than age 18y (N=214) Chart review and structure interviews	CVS by Consensus Diagnostic Criteria At least three discrete episodes of vomiting	Diagnosed with other diseases	Unknown dose and duration of treatment	Percent reduction in number of emesis or episodes	>50% reduction in vomiting in 46% in migraine-associated CVS (N=32), 0% in nonmigraine-associcated CVS (N=5)	Unknown
Boles et al.	Patients (N=62 total, 58 children) Clinical interview using questionaire	CVS by Fleisher and Li Meet 2 or more of these criteria: global cognitive delay, seizure disorder, myopathy, growth retardation, family history suspicious for maternal inheritance	Malrotation, intracerebral tumor, fetal alcohol syndrome, abnormal karyotype, metabolic disorder	Unknown dose and duration of treatment	Report per parent	Beneficial in 8 of14 patients (57%)	Unknown
Anders en et al.	Children age 2-16y (N=27)	CVS by Fleisher and Li	Organic causes	Dose 0.1-0.3 mg/kg/day	Grade response	66% (4 of 6) complete response 17% (1of6) partial	Sedative effects and weight gain in some patients; no other

CYPROHEPTADINE CVS

- NASPGHAN: Cyproheptadine - first choice in prophylaxis treatment in children younger < 5y.
- No role in acute attack

DOSAGE

- Depends on the age of the patient.
  - Age 2-6 y: 2mg 2 to 3 times daily (max of 12 mg daily)
  - Age 7-14y: 4mg 2 to 3 times daily (max of 16 mg daily)
  - Age >15y: 4 mg 3 times daily (max 0.5 mg/kg daily)
- Not been determined by RCT

DOSAGE

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ADVERSE EFFECTS OF CYPROHEPTADINE

- No major adverse effects have been reported in pediatric studies.
- Antihistaminergic effects
- Antiserotonergic effects
- Anticholinergic effects

CONCLUSIONS

- Cyproheptadine: a potentially effective and safe treatment option in children with FGIDs.
- Prescription in primary care and gastroenterology practices before resorting to expensive and invasive investigations in children if they meet the clinical criteria for FGIDs.
- Well-designed multicenter trials with long-term follow-up are needed to further investigate its efficacy in these children.

THANK YOU

REFERENCES

- Amornluck Krasaelap, MD; and Shailender Madani, MD. Cyproheptadine a potentially effective treatment for Functional Gastrintestinal Disorders in Children. Pediatric Annals•Vol.46, No. 3, 2017.

- Abbreviation: CI confidence interval, CIG complete improvement group, NIG no improvement group, PIG partial improvement group, RLQ right lower quadrant, RR relative risk, RUQ right upper quadrant, wk week, y year