



DOMPERIDONE IN THE NICU

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Disclosures

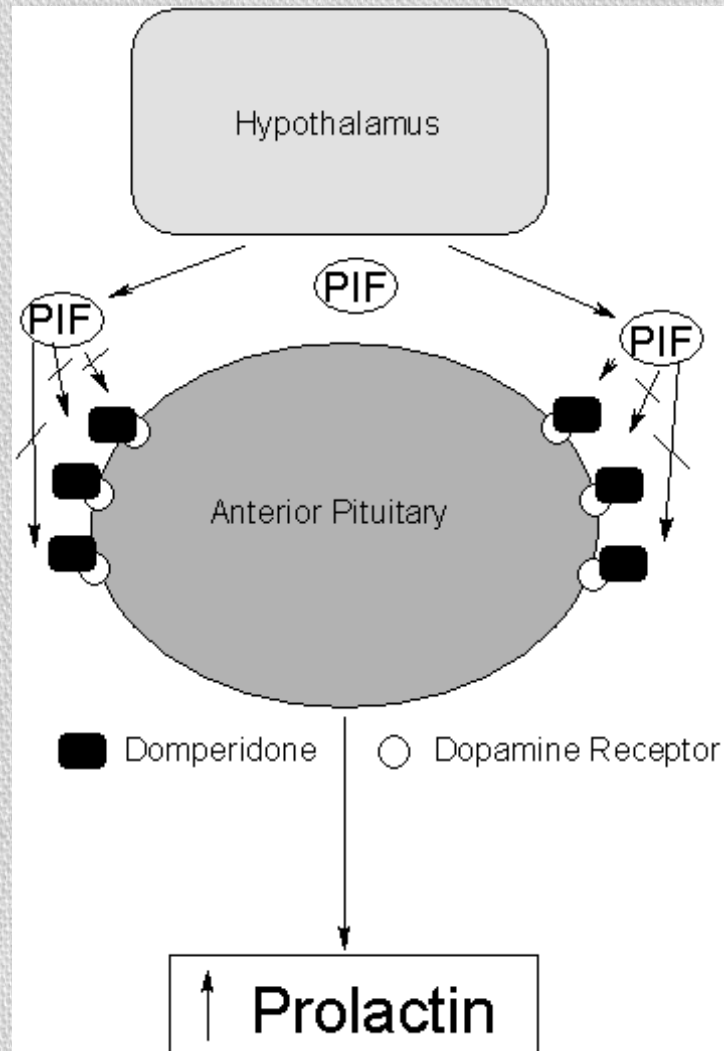
- I have no corporate interest or disclosures to announce

What does Domperidone do?

Domperidone increases the volume of breastmilk of preterm mothers experiencing lactation failure, without substantially altering the nutrient composition.



Domperidone



- Peripheral dopamine antagonist
- Upper GI motility disorders
- Blocks action of 'Prolactin Inhibiting Factor' in the anterior pituitary



DOMPERIDONE

TRADE: MOTILIUM,
MOTILIDONE

Dopamine Antagonist

Used for controlling nausea and vomiting, dyspepsia, reflux

It is a dopamine antagonist similar to Metoclopramide (Reglan)

Why is Domperidone better than Metoclopramide?

Domperidone

- Relative infant dose 0.01%-0.35%
- Does not enter the brain compartment
- Has few CNS effects

Metoclopramide

- Relative infant dose 4.7%-14.3%
- Crosses the blood brain barrier
- Infant and adult concerns have been reported such as sedation, diarrhea, extrapyramidal symptoms
- Some suggestion that an enhancing rate of colostrum to mature milk
- Dose dependent

Medications and Mothers' Milk Hale 2014

Domperidone

- LRC (Lactation Risk Category): L1 Compatible
- Drug which has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.
- $T_{1/2} = 7-14$ hours
- $T_{max} = 30$ minutes
- Oral = 13-17%
- Relative Infant Dose = 0.01% - 0.35%

The Challenges of Preterm Breastfeeding



Mothers are capable of producing milk for any viable infant, however, there are many challenges to overcome...

“Human milk is the preferred feeding for all infants, including premature and sick newborns with rare exceptions...”

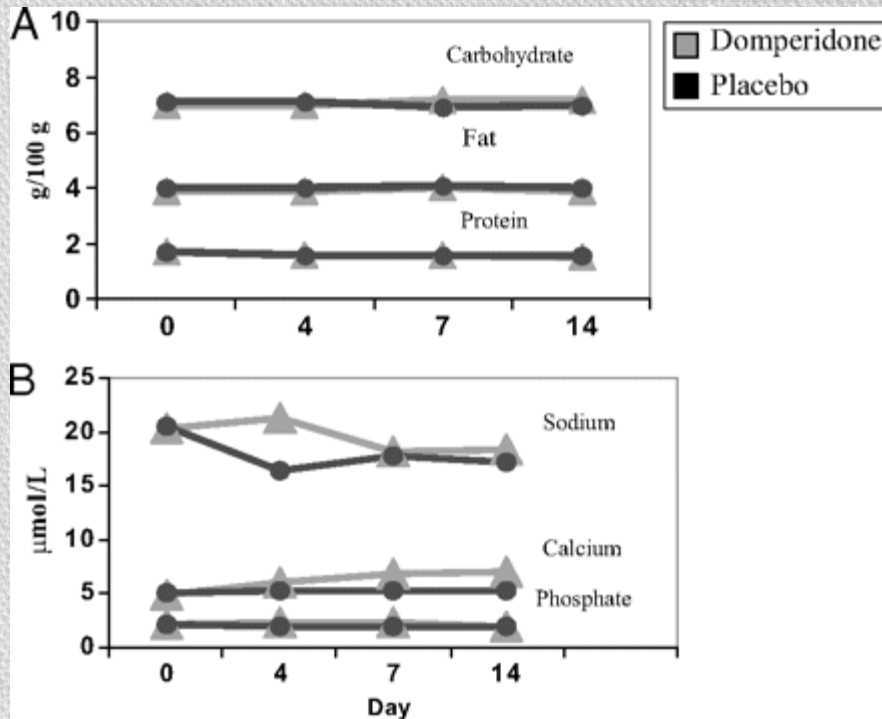
AAP Policy on Breastfeeding and the Use of Human Milk, 1997.



Breastfeeding Advantages

- Breast milk : hormones, growth factors, cytokines, living cells and immunoglobulin's
- **Preterm infants fed mothers' own milk have:**
 - Faster achievement of full enteric feeding
 - Decreased frequency and severity of infections especially late onset sepsis, NEC
 - Enhanced retinal development, visual acuity and neuro-cognitive outcomes
 - Decreased rate of BPD
 - Decreased rate of re-hospitalization after d/c
 - Economical and environmental advantages

Does the composition of breastmilk change when a mother takes domperidone?



- Energy, fat, sodium, phosphate =
- Protein > in placebo group < in Domperidone group (9.6%)
- Calcium and carbohydrates > in Domperidone group

Expressing Breastmilk in the NICU



Mothers must express their milk 8 or more times/24 hrs. Pumps try to mimic the infant at breast, but are not as efficient and do not provide the same psychological stimulus.

Mothers of Premature Babies

Increased risk of not producing an adequate milk supply

- absence of suckling and separation
- stress
- higher risk population (medical or surgical)
- may not have an effective breast pump
- milk expression may be delayed due to separation, early d/c

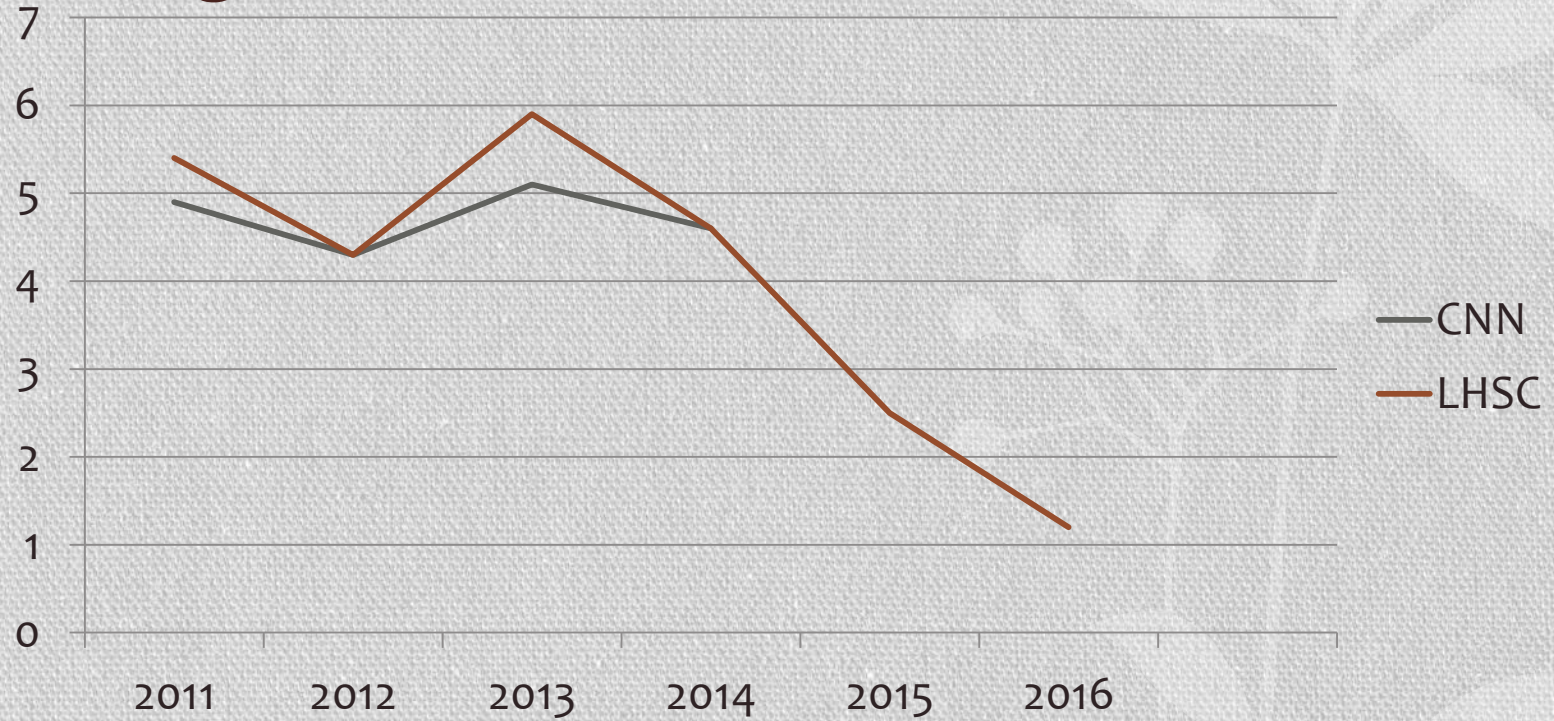


NICU Specific Lactation Care Is Required

Necrotizing Enterocolitis



NEC Stage 2 or 3



Protections with Mothers Own Milk that are Lost or Reduced in Donor Milk

- Early milk (colostrum) has a high protein content, which is protective, it is more like amniotic fld., mothers of preterm infants make preterm milk
- Stem cells survive only in fresh milk, and only for a few hours

Human Milk Pasteurization

| Component | Pasteurization |
|----------------------------|---------------------|
| Cellular | Abolished |
| Lactoferrin | 57-80% reduction |
| Interleukin - 10 | 66% reduction |
| Immunoglobulins (sIgA,IgG) | Up to 60% reduction |
| Antioxidants | Destroyed |
| Adiponectin | 33% reduction |
| Insulin | 46% reduction |
| Soluble CD14 | 88% reduction |
| IGF-1, IGF-2 | 40% reduction |
| Proteases | Different profile |
| Amylase | 15% reduction |
| Lipases (all) | Abolished |

- Ewaschuk et al., J. Appl Physiol. Nutr Metab., 2011. Underwood, Diet and Nutrition in Crital Care, 2015.

Donor Milk

Mechanisms of Protection with MOM that are Reduced or Lost in DHM

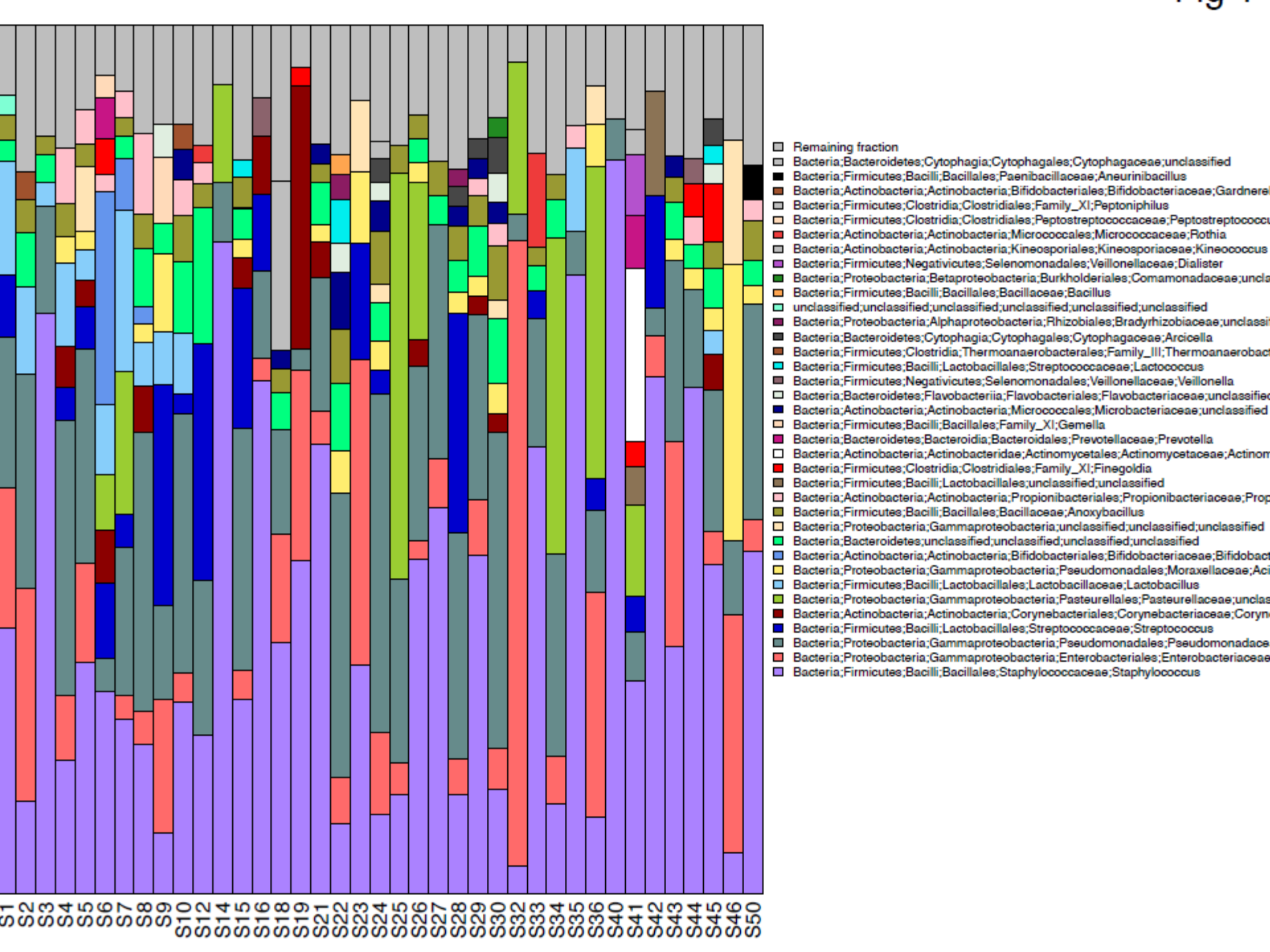
- Longitudinal changes in HM composition
- Appear to mirror the biology of the recipient infant
- Differences in mammary maturity and HM product
- PT MOM more protective with respect to most components
- Losses with freeze-thaw cycles
- Losses with pasteurization
- Losses with digestive processes
- Addition of fortifiers not tested previously with DHM

THE JOURNAL OF PEDIATRICS • www.jpeds.com

MEDICAL
PROGRESS

Donor Human Milk Update: Evidence, Mechanisms, and Priorities for Research and Practice

Paula Meier, PhD, Aloka Patel, MD, and Anita Esquerra-Zwiers, PhD(c)



How to get more milk?

- Lactation support
- Skin to skin in the NICU, open visiting, pumping at the bedside, infant based feeding readiness
- Medical support and encouragement
- Breast pumps (hospital, loaner, rentals)
- OIT and hand expression
- Education-early milk expression
- Culturally/religious individual based care plans
- PDNC f/u for NICU infants after d/c until 6 months
- Community partners – PH, Telehealth
- Continuity of care and information
- Web-sites with current regional based information
- Government recognition and support (Ont. Works, Maternity leave, BFI)
- Society trends-breastfeeding in public





DOMPERIDONE

Does it work?

Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial

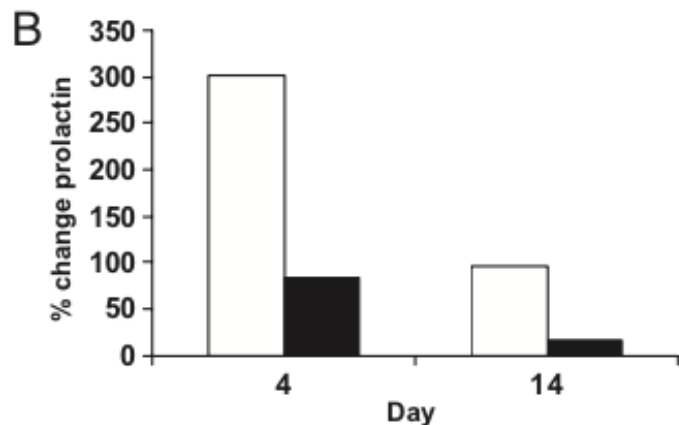
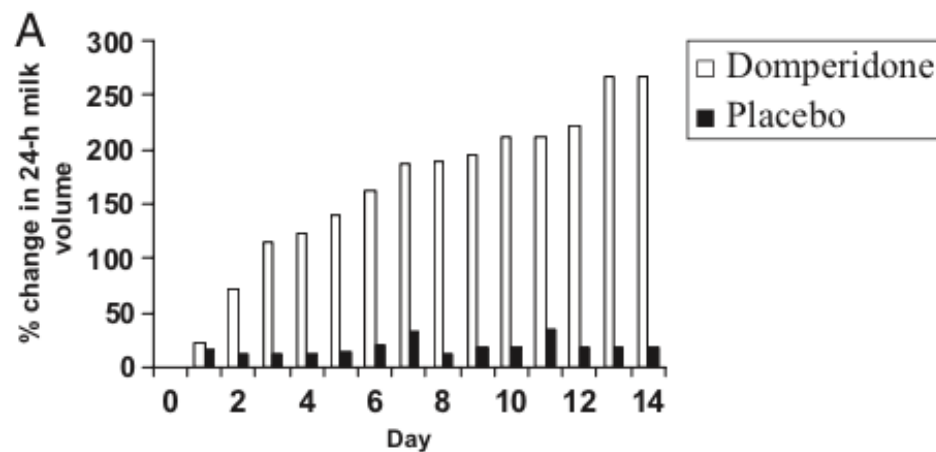
Orlando P. da Silva,^{*} David C. Knoppert,[†] Michelle M. Angelini,[‡]
Penelope A. Forret[‡]

- **Objective:** Investigate the efficacy of domperidone in augmenting milk production in mothers of premature newborns
- Randomized, double-blind, placebo-controlled trial
- 20 patients randomly assigned to receive:
 - Domperidone 10mg po TID x 7 days
 - Placebo x 7 days
- **Measured:**
 - Milk volume daily
 - Domperidone levels in randomly selected milk and serum samples on day 5
 - Serum prolactin levels prior to start of study, day 5 and day 10
- Data from 16 patients available for analysis (7 domperidone & 9 placebo)

Effect of Domperidone on the Composition of Preterm Human Breast Milk

PEDIATRICS®

AUTHORS: Marsha L. Campbell-Yeo, MN,^{a,b} Alexander C. Allen, MD,^{a,c} K. S. Joseph, MD, PhD,^{a,c,d} Joyce M. Ledwidge, PDT,^a Kim Caddell, BscN,^a Victoria M. Allen, MD, MSc,^{a,d} and Kent C. Dooley, PhD^e



- No differences between group characteristics at baseline
- By day 14, breast milk volumes increased by 267% in domperidone group vs. 18.5% in placebo group ($P = 0.005$)
- By day 14, serum prolactin levels increased by 97% vs. 17%, however, not statistically significant ($P=0.07$)

Use of domperidone as a galactagogue drug: a systematic review of the benefit risk ratio

Table 1. Main Features of the 4 Included Studies.

| Study | Study Location | Participants Domperidone/ Control, n; Type of Delivery; Term | Study Design | Domperidone Dose | Milk Volume, mL/day, mean \pm SD; Day of Measure | Prolactin Values, μ g/L, mean \pm SD; Day of Measure | Maternal Safety | Infant Safety |
|---|--|---|--|--|--|--|--|-------------------|
| Jantarsaengaram et al, 2012 ²⁰ | Obstetrics and gynecology department, Thailand | 22/23; 100% cesarean delivery; term infants | Double-blind randomized controlled trial | 10 mg orally 4 times daily for 4 days | D: 191.3 \pm 136.1; C: 91.4 \pm 60.3; day 4 | No information | D: Dry mouth (7 mothers) C: No adverse effect | No information |
| Campbell-Yeo et al, 2010 ¹² | Neonatal intensive care unit, Canada | 22/24; D: 45.5% cesarean delivery, C: 50% cesarean delivery; preterm infants < 31 weeks gestation | Double-blind randomized controlled trial | 10 mg orally 3 times daily for 2 weeks | D: 380.2 \pm 201.6; C: 250.8 \pm 171.6; day 14 | D: 81.3 \pm 70.8; C: 36.0 \pm 26.2; day 14 | D: No adverse effect C: Mild abdominal cramp (1 mother) | No adverse effect |
| Petraglia et al, 1985 ¹⁹ | Obstetrics and gynecology department, Italy | 9/8; vaginal delivery; term infants | Double-blind controlled trial | 10 mg orally 3 times daily for 10 days | D: 673 \pm 44; C: 398 \pm 45; day 10 | D: 146.9 \pm 14.8; C: 65.4 \pm 13.6; day 5 | No adverse effect | No adverse effect |
| Da Silva et al, 2001 ¹⁸ | Neonatal intensive care unit, Canada | 7/9; unknown; preterm infants | Double-blind randomized controlled trial | 10 mg orally 3 times daily for 7 days | D: 183.5 \pm 138.5; C: 66.0 \pm 61.7; day 7 | D: 119.3 \pm 97.3; C: 18.1 \pm 14.7; day 5 | No adverse effect | No adverse effect |

Abbreviations: C, control; D, domperidone.

Cochrane Library

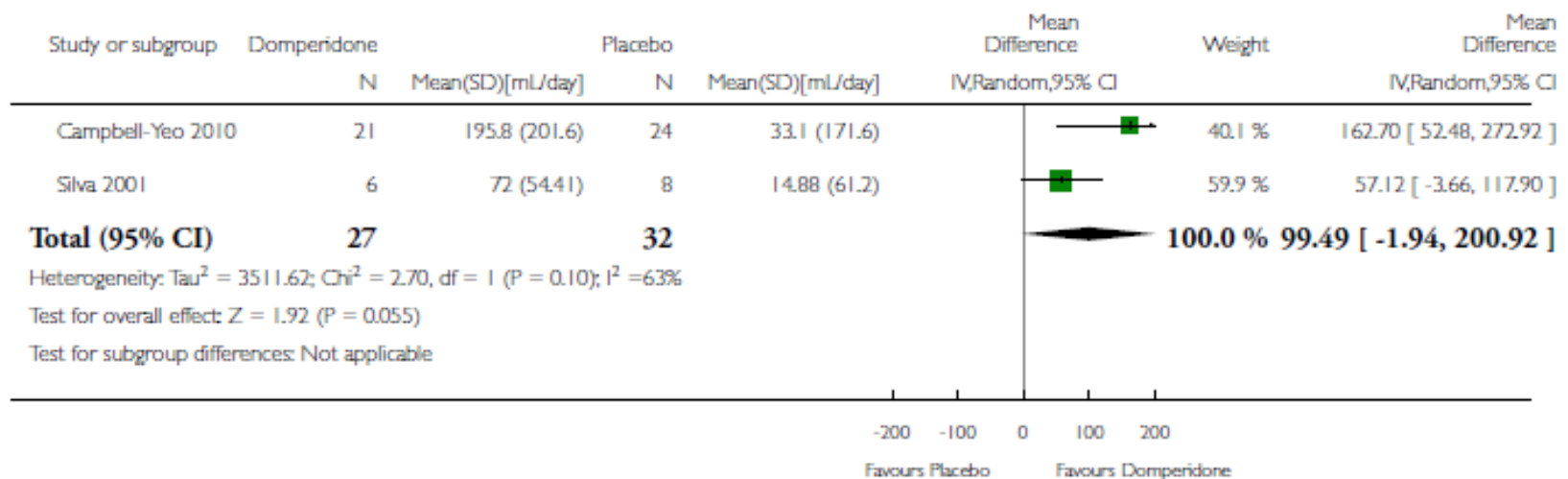
Medications for increasing milk in mothers expressing breastmilk for their preterm hospitalized infants (Review)

Analysis 1.1. Comparison 1 Domperidone versus placebo, Outcome 1 Difference in volume of EBM per day.

Review: Medications for increasing milk supply in mothers expressing breastmilk for their preterm hospitalised infants

Comparison: 1 Domperidone versus placebo

Outcome: 1 Difference in volume of EBM per day



Domperidone around the world

- Available in more than 50 countries, including:
 - Canada, Australia, Belgium, Ireland, Italy, Japan, United Kingdom, the Netherlands (many countries domperidone is over-the-counter)
- Not available:
 - United States of America
 - *Exception: Available via an Investigational New Drug Application (IND) for severe GI disorders refractory to standard therapy.*



So what's the problem?

Not all of the concerns were addressed and sample sizes were small



Health Canada Warning

- Domperidone may be associated with a small increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients:
 - older than 60 years of age;
 - using daily doses greater than 30 mg;
 - having predisposing factors for QT prolongation including concomitant use of QT-prolonging drugs or CYP 3A4 inhibitors.
- Domperidone is now contraindicated in patients:
 - with prolongation of cardiac conduction intervals, particularly QT;
 - with significant electrolyte disturbances;
 - with cardiac disease (such as congestive heart failure);
 - with moderate or severe liver impairment;
 - receiving QT-prolonging drugs and potent CYP3A4 inhibitors.
- Domperidone should be used at the lowest effective dose to a maximum recommended daily dose of 30 mg and for the shortest possible duration.

A Consensus Statement on the Use of Domperidone To Support Lactation

- May 11th, 2012 **Authors:** Daniel Flanders, Aviva Lowe, Michael Kramer, Orlando da Silva, Carole Dobrich, Marsha Campbell-Yeo, Edith Kernerman, Jack Newman

Empower Study

Enhancing Human Milk Production With Domperidone in Mothers of Preterm Infants: Results From the EMPOWER Trial

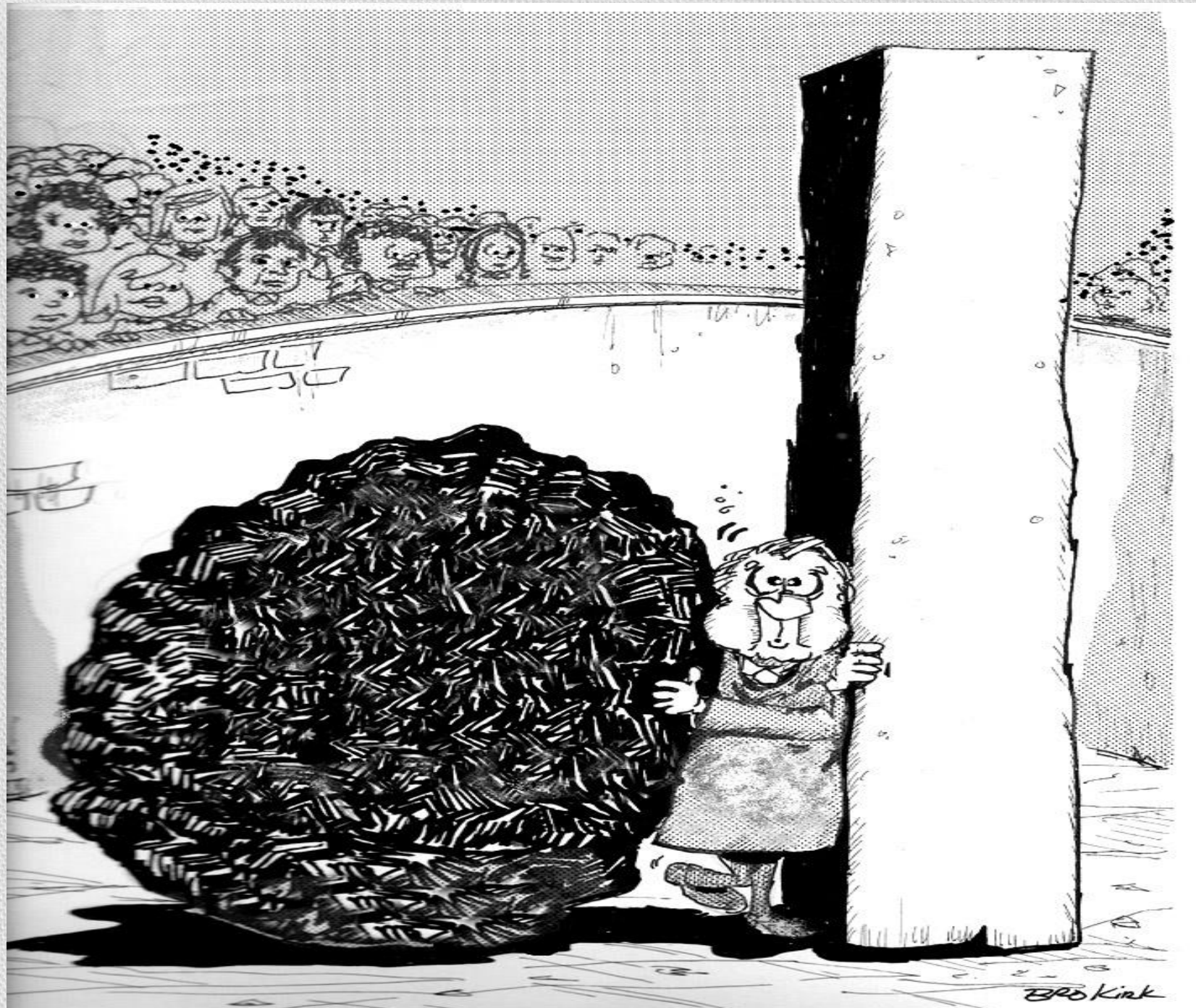
- Recruitment based on infants weight vs. total volume pumped
- Mothers wanted the drug not chancing a placebo

Summary Safety Review - DOMPERIDONE - Serious abnormal heart rhythms and sudden death

- There is evidence suggesting a link between the use of domperidone and the development of serious abnormal heart rhythms and sudden death. Risks are increased (i) in patients taking domperidone at doses greater than 30 mg a day, (ii) in patients over 60 years of age, and (iii) in patients taking domperidone together with drugs that can lead to increased domperidone blood levels or with drugs that are known to affect the electrical activity of the heart. This safety information applies to patients taking domperidone for any conditions.

Health Canada Warning





Empower

Key Messages

- There is a paucity of research to best guide clinicians as to dose, timing of administration, and duration of treatment of domperidone in mothers of preterm infants.
- Domperidone was effective in supporting more mothers to increase their milk volume starting as early as 8 days post-delivery.
- Staring mothers on domperidone 2 weeks later was similarly effective in supporting mothers to increase their milk volume.
- No serious adverse effects or evidence of prolonged Q-Tc were observed in this study.

Domperidone

Is it now safe out there?



COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)



Crediblemeds.org is your trusted partner providing reliable information on medicines. This is a combined list of drugs that CredibleMeds has concluded either 1) have a risk of TdP, 2) prolong QT and therefore have a possible risk of TdP or 3) have a risk of TdP under certain conditions such as overdose, drugdrug interactions or when administered to certain high-risk individuals (e.g. congenital long QT syndrome).

| Generic Name | Brand Name |
|------------------|--|
| Alfuzosin | Uroxatral® |
| Amantadine | Symmetrel® and others |
| Amiodarone | Cordarone® and others |
| Amisulpride | Solian® and others |
| Amitriptyline | Elavil® (Discontinued 6/13) and others |
| Amoxapine | Asendin® and others |
| Anagrelide | Agrylin® and others |
| Apomorphine | Apokyn® and others |
| Aripiprazole | Abilify® and others |
| Arsenic trioxide | Trisenox® |
| Astemizole | Hismanal® |
| Atazanavir | Reyataz® |
| Atomoxetine | Strattera® |
| Azithromycin | Zithromax® and others |
| Bedaquiline | Sirturo® |
| Bepridil | Vascor® |
| Bortezomib | Velcade® and others |
| Bosutinib | Bosulif® |
| Chloral hydrate | Aquachloral® and others |
| Chloroquine | Aralen® |
| Chlorpromazine | Thorazine® and others |
| Cilostazol | Pletal® |
| Ciprofloxacin | Cipro® and others |
| Cisapride | Propulsid® |
| Citalopram | Celexa® and others |
| Clarithromycin | Biaxin® and others |
| Clomipramine | Anafranil® |
| Clozapine | Clozaril® and others |
| Cocaine | Cocaine |
| Crizotinib | Xalkori® |

| Generic Name | Brand Name |
|--------------------------------|------------------------|
| Dabrafenib | Tafinlar® |
| Dasatinib | Sprycel® |
| Desipramine | Pertofrane® and others |
| Dexmedetomidine | Precedex® and others |
| Dihydroartemisinin+piperaquine | Eurartesim® |
| Diphenhydramine | Benadryl® and others |
| Disopyramide | Norpace® |
| Dofetilide | Tikosyn® |
| Dolasetron | Anzemet® |
| Domperidone | Motilium® and others |
| Donepezil | Aricept® |
| Doxepin | Sinequan® and others |
| Dronedarone | Multaq® |
| Droperidol | Inapsine® and others |
| Eribulin | Halaven® |
| Erythromycin | E.E.S.® and others |
| Escitalopram | Cipraxel® and others |
| Famotidine | Pepcid® and others |
| Felbamate | Felbatol® |
| Fingolimod | Gilenya® |
| Flecainide | Tambocor® and others |
| Fluconazole | Diflucan® and others |
| Fluoxetine | Prozac® and others |
| Foscarnet | Foscavir® |
| Furosemide (Frusemide) | Lasix® and others |
| Galantamine | Reminyl® and others |
| Gatifloxacin | Tequin® |
| Gemifloxacin | Factive® |
| Granisetron | Kytril® and others |
| Grepafloxacin | Raxar® |

| Generic Name | Brand Name |
|--------------------------|------------------------------|
| Halofantrine | Halfan® |
| Haloperidol | Haldol® (US & UK) and others |
| Hydrochlorothiazide | Apo-Hydro® and others |
| Hydroxychloroquine | Plaquenil® and others |
| Hydroxyzine | Atarax® and others |
| Ibutilide | Corvert® |
| Iloperidone | Fanapt® and others |
| Imipramine (mepipramine) | Tofranil® |
| Indapamide | Lozol® and others |
| Isradipine | Dynacirc® |
| Itraconazole | Sporanox® and others |
| Ivabradine | Procoralan® and others |
| Ketoconazole | Nizoral® and others |
| Lapatinib | Tykerb® and others |
| Levofloxacin | Levaquin® and others |
| Levomethadyl acetate | Oriaam® |
| Lithium | Eskalith® and others |
| Mesoridazine | Serentil® |
| Methadone | Dolophine® and others |
| Metoclopramide | Reglan® and others |
| Metronidazole | Flagyl® and many others |
| Mifepristone | Korlym® and others |
| Mirabegron | Myrbetriq® |
| Mirtazapine | Remeron |
| Moexipril/HCTZ | Uniretic® and others |
| Moxifloxacin | Avelox® and others |
| Nelfinavir | Viracept® |
| Nicardipine | Cardene® |
| Nilotinib | Tasigna® |
| Norfloxacin | Noroxin® and others |

| Generic Name | Brand Name |
|-------------------------------|----------------------------|
| Nortriptyline | Pamelor® and others |
| Ofloxacin | Floxin® |
| Olanzapine | Zyprexa® and others |
| Ondansetron | Zofran® and others |
| Oxytocin | Pitocin® and others |
| Paliperidone | Invega® and others |
| Pantoprazole | Protonix® and others |
| Paroxetine | Paxil® and others |
| Pasireotide | Signifor® |
| Pazopanib | Votrient® |
| Pentamidine | Pentam® |
| Perflutren lipid microspheres | Definity® |
| Pimozide | Orap® |
| Pipamperone | Dipiperon (E.U) and others |
| Posaconazole | Noxafil® and others |
| Probucol | Lorelco® |
| Procainamide | Pronestyl® and others |
| Promethazine | Phenergan® |
| Propofol | Diprivan® and others |
| Protriptyline | Vivactil® |
| Quetiapine | Seroquel® |
| Quinidine | Quinaglute® and others |
| Quinine sulfate | Qualaquin® |
| Ranolazine | Ranexa® and others |
| Rilpivirine | Edurant® and others |
| Risperidone | Risperdal® |
| Ritonavir | Norvir® |
| Roxithromycin | Rulide® and others |
| Saquinavir | Invirase®(combo) |

| Generic Name | Brand Name |
|-------------------------|---|
| Sertindole | Serdolect® and others |
| Sertraline | Zoloft® and others |
| Sevoflurane | Ulane® and others |
| Solifenacin | VESIcare® |
| Sorafenib | Nexavar® |
| Sotalol | Betapace® and others |
| Sparfloxacin | Zagam® |
| Sulpiride | Dogmatil® and others |
| Sunitinib | Sutent® |
| Tacrolimus | Prograf® and others |
| Tamoxifen | Nolvadex®(discontinued 6/13) and others |
| Telaprevir | Incivek® and others |
| Telavancin | Vibativ® |
| Telithromycin | Ketek® |
| Terfenadine | Seldane® |
| Tetrabenazine | Nitoman® and others |
| Thioridazine | Mellaril® and others |
| Tizanidine | Zanaflex® and others |
| Tolterodine | Detrol® and others |
| Toremifene | Fareston® |
| Torseamide (Torasemide) | Demadex® and others |
| Trazodone | Desyrel® (discontinued 6/13) and others |
| Trimipramine | Surmontil® and others |
| Vandetanib | Caprelsa® |
| Vardenafil | Levitra® |
| Vemurafenib | Zelboraf® |
| Venlafaxine | Effexor® and others |
| Voriconazole | VFend® |
| Vorinostat | Zolinza® |
| Ziprasidone | Geodon® and others |

Milk Volume

Lactation Support/Compliance



- A mother who has an infant in the NICU and has not received proper lactation support or who is non compliant (milk expression) is **not** a good candidate to receive a galactagogue such as Domperidone

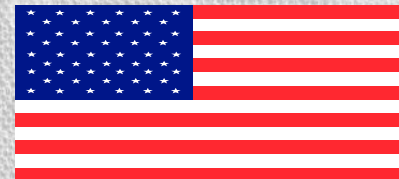
What else?

- Domperidone should not be used where the mother or the infant has a cardiac disorder
- Current mastitis
- Chronic illness
- Gastric abnormalities, gastric bypass surgery
- And caution with nicotine users
- Discuss risks
- Ongoing monitoring and support should continue while on Domperidone and after as necessary

Thomas Hale

“Medication and Mother’s Milk”

“It is approved for use in all the worlds largest and finest countries, including England, Australia, Canada, etc. This warning from the FDA has nothing to do with its safety, its all about the importation of drugs from Canada and control by this federal agency.”



Conclusion

- Mothers with infants in the NICU are at a much higher risk of lactation failure
- A galactagogue that does not risk a prolonged QTc interval would be ideal
- Domperidone remains a better choice than metoclopramide
- Herbals are not evidence based and strength/source of herb is sometimes in question
- Donor milk remains a better choice than formula, but is still not ideal as it lacks many important components available in just expressed mothers own milk

A detailed milk record and Lactation Consultant support is an essential part of the care plan for mothers who are on Domperidone or considering taking it

Conclusions: Domperidone Dosage

- 1) An increased dose of domperidone appears to produce a clinical increase in milk supply.
- 2) Twice daily dosing of domperidone may be adequate to produce clinically relevant increases in breast milk.
- 3) Common daily doses presently seen-
 - 10mg TID
 - 10mg QID
 - 10-20mg TID

Prescribe at the lowest possible dose and continue to follow lactation success in order to wean domperidone as soon as possible

Domperidone remains the only viable option for woman who require help with their milk supply and have exhausted ***all*** other options to increase their volume.



Future Studies

- Is twice daily dosing adequate?
- What is the optimal duration of therapy with domperidone ?
- Are increased doses and prolonged duration of domperidone therapy safe to mother and baby?

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Thank you

- Liz Burrill
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*And the moms and their baby's
that have taught me so much
over the years*





Thank you for your attention...