DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Seventh, Jul-Sep 2022

Dear Readers,
The purpose of this bulletin is to disseminate some important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights the various pharmacological aspects of medicine use during breastfeeding and recent drug approvals by FDA. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

World Breastfeeding Week: 1– 7 August 2022

Medicine Use in Lactation

Medicines are often needed by women who are breastfeeding. Due to lack of, or ambiguous, information about the safety of medicines transferred to the infant in breast milk, often breastfeeding has been stopped unnecessarily or a different, potentially less appropriate treatment prescribed. Although most medicines are excreted in breast milk to some degree, the amount is usually less than 10% of the maternal dose. Medicines excreted at less than 10% are considered compatible with breastfeeding. Therefore, with a few exceptions the majority of medicines may be used during breastfeeding.

Examples of drugs contraindicated in breastfeeding

Drug	Comment(s)
Amiodarone	Long half-life, iodine-containing molecule, and may affect thyroid function in infant
Antineoplastics	Leukopenia, bone marrow suppression
Gold salts	Rash, nephritis, haematological abnormalities
Iodine	High doses (>150 micrograms daily) lead to risk of infant hypothyroidism
Lithium	Breastfeeding only feasible with rigorous monitoring
Radiopharmaceuticals	Stunted growth, deformities, abnormal brain function, or cancer; most sensitive to radiation from 2 to 18 weeks of pregnancy
Retinoids (oral)	Potential for serious adverse effects

Drugs used to stimulate milk production (Galactogogues)

-Domperidone
-Metoclopramide
-Chlorpromazine
-Growth hormone
-TRH
-Oxytocin
-Herbal products
(Non-pharmacological approaches to boost milk supply, such as correct advice, support and more frequent breastfeeding, are preferable.)

Drugs inhibiting Lactation

-Dopamine agonist:
Bromocriptine
Cabergoline
-Diuretics: Loop, thiazide
-Ergotamine
-Calcitonin
-Levodopa
-Contraceptives
-Pseudoephedrine
-Tamoxifen

Key points

- Most medicines may be safely used during breastfeeding (the lowest effective dose for the shortest possible duration should be used).
- Physicochemical characteristics of the medicine and breast milk composition determine the concentration of medicines in breast milk.
- Adverse reactions more commonly observed in nursing infants include sedation, gastrointestinal upset and irritability.
- The benefits and risks of harm of treatment in both the mother and infant should be considered as well as the benefits and risks of harm of not treating.

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What affects the concentration of a drug in milk?

Almost all medicines pass into breast milk but the drug concentration achieved is dependent on a number of factors as mentioned below:-

Factors	Comment(s)
Maternal plasma concentration	-Passive diffusion is the primary pathway by which drugs enter milk. -Good concordance between the time-course of maternal plasma-drug concentration and milk-drug concentration. -Maternal plasma concentration is also affected by the drug's distribution into different tissues. e.g. A high volume of distribution (as for sertraline) will contribute to a lower maternal plasma concentration and a subsequent lower concentration in milk.
Maternal plasma protein binding	-Transfer into breast milk is also influenced by the extent to which the drug is bound by maternal plasma proteins. -Free unbound drug diffuses readily while highly protein-bound drugs like ibuprofen or warfarin (both 99% protein bound) are unable to diffuse in significant amounts. -Sertraline is highly protein bound (98%) so overall it will be minimally transferred to the breastfed baby. By comparison, venlafaxine has much lower protein binding and so more drug will be present in milk.
Size of the drug molecule	-Most drug molecules, including alcohol, nicotine and caffeine, are small enough to enter milk. -Exceptions are drugs with high molecular weights such as heparins and insulin.
Degree of ionization	-Drugs cross membranes in an un-ionized form. Milk is generally slightly more acidic (pH 7.2) than the mother's plasma (pH 7.4) so it attracts weak organic bases such as oxycodone and codeine. -Such drugs become ionized and 'trapped' in the milk. -Conversely, weak organic acids such as penicillin tend to be ionized and held in maternal plasma.
Lipid solubility	-In addition to the passive diffusion, lipid-soluble drugs such as citalopram may have co-secretion by dissolution in the fat droplets of milk. -Not clinically relevant, not an indication to change therapy if citalopram has been effective, but infant drowsiness should be monitored. -Although the fat content of the milk varies according to infant age and phase of the feed, this is unlikely to impact the choice of drug therapy.
Maternal phamacogenomics	-A growing understanding of the influence of pharmacogenomics is well exemplified with codeine which is variably metabolized to morphine by the cytochrome P450 (CYP) 2D6 enzyme. -Repeated codeine doses in these women produce significant amounts of morphine. -Rapid transfer from maternal plasma to the milk may result in central nervous system depression and potentially infant death. -Codeine should be avoided during breastfeeding and alternative analgesia is recommended, such as paracetamol or ibuprofen.

Drugs like dopamine agonists (eg, bromocriptine), decongestants, and estrogens (eg, in hormonal contraceptives) decrease breast milk volume. Consider alternative medications if a mother is taking these medications and has compromised breast milk supply.

What influences the risk of adverse effects on the baby?

If the baby is exposed to a drug in milk, several factors ,as mentioned in table below, will determine if there is an effect.

Factors	Comment(s)
Timing of the dose	Feeding the baby just before the mother takes a drug results in the baby receiving the lowest possible drug concentration (does not apply for drugs with a long half-life, such as diazepam).
Toxicity	-Premature babies and neonates have a lower capacity to metabolize and excrete drugs. In addition, for babies who may already have been exposed to a drug in utero just before delivery, further exposure via breast milk will augment the existing drug concentration. -Some drugs are inappropriately regarded as unsafe. Metronidazole, despite unfounded fears of carcinogenicity and mutagenicity, is safe in breastfeeding for short-term use. However, bitter taste in milk may lead to fussiness in the feeding infant. -Valproate is regarded as safe, especially in monotherapy when the risk of infant sedation is low. Monitoring the infant for liver and platelet changes may be advisable. -The immunosuppressant azathioprine is excreted into breast milk as an active metabolite 6-mercaptopurine. Cautious use is advised in lactating women, and monitoring of the infant for signs of immunosuppression and other toxicity is recommended.
Oral bioavailability	The drug's presence in breast milk does not necessarily lead to significant exposure for the baby. The infant gut may degrade or destroy a drug,e.g. omeprazole (for which the standard formulation is enteric-coated). Gentamicin is given intravenously to the mother. As it is poorly absorbed orally by the baby, drug concentrations will not be reflected in infant plasma.
Volume of breast milk	The amount of milk a baby receives varies. The estimated intake by an exclusively breastfed baby is 150 mL/kg/day. However, if the breast is being offered only as a comfort to an older baby, for example at night, the volume ingested is likely to be small.
Relative infant dose	Relative infant dose is the dose received via breast milk (mg/kg/day) relative to the mother's dose (mg/kg/day). A relative dose of 10% or above is the notional level of concern, but this is rare. An example is lithium, which is generally contraindicated in breastfeeding.
Age of infant	Most adverse effects of drugs in breast milk occurred in newborns under two months and rarely in those above six months. An infant's metabolism and excretion capacity at birth is only a third of what it is at 7–8 months.

Advice on social drugs

-Advise mothers to avoid alcohol. A breastfeeding woman should avoid exposing the infant to alcohol by waiting to nurse for two hours after a single serving of alcohol (12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof liquor). If a woman drinks more than this amount, she should refrain from breastfeeding for an additional two hours for each serving of alcohol.

-Nicotine replacement therapy is not an absolute contraindication to breastfeeding and is preferable to smoking, although short-acting forms should be selected. Smoking, including passive smoking, has been associated with sudden infant death syndrome.

-High maternal intake of caffeine is associated with irritability & poor sleep patterns in the infant.

-Cannabis exposure causes impairment in motor development of infant.

A women may be affected by a range of health issues like infection, pain, contraception, low milk supply, depression and atopic conditions during postpartum period. Below table provides information on the compatibility of medicines used in the treatment of these conditions with breastfeeding.

Compatibility of commonly used medicines with breastfeeding

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Infection	***Antibiotics***		
	β-lactams (e.g., amoxicillin)	Compatible	Gastrointestinal flora changes possible; monitor infant for diarrhoea, vomiting, thrush
	Macrolides (e.g., erythromycin)	Compatible	Single dose of azithromycin considered safe
	Cephalosporins (e.g., cephalexin)	Compatible	May also affect infant gut flora (third generation more likely)
	Fluoroquinolones (e.g., ciprofloxacin)	Avoid if possible	Potential risk of arthropathies
	Trimethoprim	Compatible	
	Nitrofurantoin	Compatible	Avoid nitrofurantoin if infant less than one month old or premature
	Metronidazole	Avoid if possible	If single 2 g metronidazole dose given, discontinue breastfeeding for 12 hours
	Antifungals		
	Azoles (e.g., fluconazole)	Compatible	If applying miconazole oral gel to nipples, apply after breastfeeding
	Nystatin	Compatible	
	Antivirals		
	Acyclovir	Compatible	
Depressive disorders	***Antidepressants***		
	SSRIs (e.g., paroxetine)	Compatible	Paroxetine and sertraline preferred due to shorter half-lives
	TCAs (e.g., amitriptyline)	Less preferred due to potential toxicity	Amitriptyline compatible in doses up to 150 mg/day
	Anxiolytics		
	Benzodiazepines (e.g., temazepam)	Compatible in a single dose; avoid repeated doses	Short-acting benzodiazepines preferred as accumulation may occur, monitor infant for drowsiness

LactMed: produced by National Library of Medicine, is a freely accessible, well-resourced and peer-reviewed online database that can be downloaded as an app for mobile devices. It is updated to keep pace with new information, including published studies and drug approvals.

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Pain	***Analgesics***		
	Paracetamol	Compatible	Paracetamol analgesic of choice
	NSAIDs (e.g., ibuprofen)	Compatible	Avoid breastfeeding with long-term acetylsalicylic acid treatment
	Opiates (e.g., codeine)	Compatible in occasional doses	Monitor infant for drowsiness, apnoea, bradycardia and cyanosis Use codeine with caution in rapid metabolizers
	Tramadol	Compatible	
Contraception	***Hormonal methods***		
	Progesterone	Compatible	
	Oestrogen	Avoid if possible	May inhibit lactation
Allergies and hay fever	***Antihistamines***		
	Sedating (e.g., promethazine)	Probably compatible	Occasional use probably safe Monitor for sedation in mother and infant
	Non-sedating (e.g., loratadine)	Compatible	
	Topical		
	Corticosteroids (e.g., hydrocortisone)	Compatible	If applying to breasts apply after feeding
Asthma	β2- adrenergics (e.g., salbutamol)	Compatible	
	Corticosteroids (e.g., budesonide)	Compatible	
Other	Warfarin	Compatible	
	Metformin	Compatible	

Practice points for prescribing in breastfeeding

- If a drug is needed, use the lowest effective dose. Temporarily suspend breastfeeding (and express milk) for potentially toxic drugs, such as cytotoxics and radiopharmaceuticals. Reinstatement of a drug will be determined by its half-life. It may not be possible to continue breastfeeding if lengthy treatment with a toxic drug is needed.
- Select alternative routes or products to minimize systemic exposure in the mother.
- Choose drugs with a relatively short half-life, such as sertraline rather than fluoxetine, to minimize drug exposure in milk.
- Advise the mother to feed the infant before taking her medicine so that the drug concentration in milk will be at its lowest (not apply to drugs with a long half-life).

National list of Essential Medicines (NLEM) 2022

The NLEM 2022 was released by MoHFW on 13 Sep 2022, contains 384 medicines. This will replace the NLEM 2015.

Weblink: https://main.mohfw.gov.in/newshighlights-104

Emerging Therapies: Changing the Melanoma Treatment Landscape

- **High dose IL-2**: First immunotherapy for metastatic melanoma approved by the FDA in 1998. However, the potential for severe toxicities from IL-2 treatment has resulted in development of newer products with less toxic effects.
- **BRAF inhibitor and MEK inhibitor**: Approximately 50% of all melanomas demonstrate a mutation in the BRAF gene and the *MEK* gene (and encoded MEK protein) interacts with the BRAF proteins aiding in cell growth. Drugs targeting the inhibition of MEK proteins are a common therapy for patients with malignant melanoma and *BRAF* mutations. Targeted therapies for inhibition of the BRAF and/or MEK proteins include **binimetinib**, **encorafenib**, **dabrafenib** , **trametinib**, **vemurafenib**, and **cobimetinib**. Additionally, combining a BRAF inhibitor and a MEK inhibitor is a common approach in treating a patient with a BRAF mutation as the combination often works better than monotherapy.
- **Immune checkpoint inhibitors**: Unlike targeted therapies, which go after melanoma cells directly, immunotherapy aims to improve the immune system's ability to identify and destroy melanoma cells. e.g. PD-1 inhibitors **pembrolizumab** and **nivolumab** and CTLA-4 inhibitor **ipilimumab**. These drugs actively block proteins involved in decreasing T-cell identification and destruction of melanoma cells. Further, blocking these proteins allows T cells to attack melanoma cells more effectively on their own.
- **Additional immunotherapies:** Melanoma vaccines and cell therapy utilizing tumor-infiltrating lymphocytes are being studied and in development phase.
- Effective immunotherapy options for treating advanced melanoma include combination **ipilimumab/nivolumab**, PD-1 inhibitor monotherapy, and most recently **relatlimab/nivolumab** fixed-dose combination.
- On March 18, 2022, the FDA approved **nivolumab** and **relatlimabrmbw** for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.
- Nivolumab and relatlimab-rmbw is a combination immunotherapy treatment of the PD-1 inhibitor nivolumab with the novel LAG-3–blocking antibody relatlimab, the combination of which has been shown to increase T-cell activation.
- When used in treatment, nivolumab and relatlimabrmbw are given as a 30 minute intravenous infusion every 4 weeks or until disease progression.
- New and emerging treatments are costly.

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34 Medicines added to NLEM 2022: Amikacin, Bedaquiline, Benda-mustine, Buprenorphine, Cefuroxime, Dabigatran, Daclatasvir, Delamanid, Dolutegravir, Fludrocortisone, Glargine, Irinotecan, Itraconazole, Ivermectin, Latanoprost, Meropenem, Montelukast, Teneligliptin, Valganciclovir etc.

New Treatment Options Are on the Horizon for β-Thalassemia

- β-Thalassemia has limited treatment options, mainly managed with red blood cell transfusions at regular intervals, generally every 2 to 4 weeks, and chelation therapy with deferoxamine or deferasirox to remove excess iron from the bloodstream.
- Currently, the only curative treatment for β-thalassemia major is a stem cell transplant.
- In late 2019, **luspatercept-aamt** became the first drug approved for treatment of anemia in adult patients with β thalassemia who require regular red blood cell transfusions.
- Approval of luspatercept-aamt was supported by the BELIEVE trial (NCT02604433), a phase 3 multicenter, randomized, double-blind, placebo-controlled trial in which the primary end point of 33% reduction or more from baseline in transfusion burden from weeks 13 to 24 was met, with 21.4% of patients in the luspaterceptaamt arm achieving this compared with 4.5% of patients in placebo.
- Most common adverse effects (AEs) associated with luspatercept-aamt include headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, nausea, trouble breathing, thromboembolic events and hypertension.
- **Gene Therapy:** Although luspatercept-aamt has been a great advancement in the treatment of transfusion-dependent β-thalassemia, a need remains for therapies that can eliminate the need for transfusions and cure the disease. Two gene therapies in late-stage development may soon provide hope for a cure.
- **Betibeglogene autotemcel:** 1-time ex vivo gene therapy for adults, adolescents, pediatric patients with all genotypes (β 0 β0 and non-β0/β0) of transfusion-dependent β-thalassemia.
- Treatment with betibeglogene autotemcel involves extraction of patient's stem cells, introduction of functional copies of a modified form of the β-globin gene (βA[T87Q]-globin gene) into the stem cells via a BB305 lentiviral vector, and infusion of the modified cells into the patient.
- With a functioning β A(T87Q) globin gene, patient should then be able to produce their own functional gene therapy–derived adult hemoglobin and no longer need RBC transfusions.
- In the phase 3 NorthStar-2 trial (NCT02906202) investigating betibeglogene autotemcel, 23 adult and pediatric patients with non-β 0/β0 genotypes were treated with betibeglogene autotemcel. In total, there were 22 patients who were eligible for evaluation, and 20 of them achieved transfusion independence, including 6 of 7 patients under age 12 years.
- Currently, betibeglogene autotemcel is approved in the European Union, United Kingdom, Iceland, Liechtenstein, and Norway for patients 12 years and older with transfusion-dependent β-thalassemia who are eligible for stem cell transplant but do not have an available donor. Further, the Innovator Company has submitted a biologics license application (BLA) to the FDA and granted priority review.

- **CTX001** is a gene therapy in phase 3 clinical trials, co-developed by CRISPR Therapeutics and partner Vertex. Like betibeglogene autotemcel, it is a 1-time ex vivo treatment but targets an increase in production of fetal hemoglobin via CRISPR/Cas9 editing of the BCL11A gene in the patient's cells. Interim data from 10 adult and pediatric patients with varying genotypes enrolled in the VX21-CTX001-141 trial (NCT05356195) demonstrated increased hemoglobin and fetal hemoglobin after administration of CTX001. During the trial, all 10 patients were able to stop transfusions within 2 months of treatment. CRISPR Therapeutics and Vertex plan to submit a BLA to the FDA in late 2022.

Potential Limitations of Gene Therapy for β-Thalassemia

Reports of myeloid malignancies following treatment with betibeglogene autotemcel for sickle cell disease, although the gene therapy has not been directly implicated in causing the malignancies. Even though patients with sickle cell disease and transfusion-dependent β-thalassemia have increased risk of developing myeloid malignancies irrespective of treatment with gene therapy, this remains an area of concern. In addition to safety concerns, cost may be a barrier to accessing gene therapy for patients with β-thalassemia (e.g. $1.8 million in Europe).

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26 Medicines deleted from NLEM 2015: Alteplase, Atenolol, Capreomycin, Chlorpheniramine, Diloxanide furoate, Dimercaprol, Erythromycin, Ethinylestradiol, Ganciclovir, Kanamycin, Leflunomide, Methyldopa, Pentamidine, Procarbazine, Ranitidine, Rifabutin, Sucralfate etc.

FDA Approves Ibrutinib for Pediatric Patients With Chronic Graft-Versus-Host Disease

The FDA has approved ibrutinib (Imbruvica)for the treatment of younger patients (1 year of age and older) with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy. The approval is the first pediatric indication for ibrutinib and the new oral suspension formulation for patients aged 1 to less than 12 years makes ibrutinib the first therapy to gain FDA approval for younger patients who had no prior treatment options for cGVHD. Ibrutinib is a once-daily oral medication that blocks the Bruton's tyrosine kinase (BTK) protein, which is necessary for normal and abnormal B cells to multiply and spread. By blocking BTK, ibrutinib can help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs. Ibrutinib was first approved by the FDA in 2013 and is currently indicated for adult patients in 6 disease areas, including 5 hematologic cancers.

Milvexian Met Primary Endpoints for Thromboembolic Diseases in Phase 2 Study

Oral factor XIa (FXIa) inhibitor milvexian, when combined with background platelet therapy, was shown to reduce the relative risk of recurrent symptomatic ischemic strokes by 30% among patients with an acute non-cardioembolic ischemic stroke or transient ischemic attack. The results of the phase 2 AXIOMATIC trials showed that FXIa inhibitors may reduce vascular event risk without increasing the risk of bleeding.

New Drugs Corner

Olipudase alfa
MoA: A hydrolytic lysosomal sphingomyelin-specific enzyme
Indication: To treat Acid Sphingomyelinase Deficiency

Spesolimab-sbzo
MoA: interleukin-36 receptor antagonist
Indication: To treat generalized pustular psoriasis flares

DaxibotulinumtoixnA-lanm
MoA: A novel Botulinum toxin type A product containing highly purified 150-kDa core neurotoxin
Indication: To treat moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity

Deucravacitinib
MoA: inhibits tyrosine kinase 2 (TYK2) via an allosteric mechanism
Indication: To treat moderate-to-severe plaque psoriasis

Eflapegrastim
MoA: Long-acting recombinant human granulocyte-colony stimulating factor (rhG-CSF)
Indication: To decrease the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs with febrile neutropenia
Reference: FDA

The Pill Box Quiz: 07

Instructions:
1. Scan the QR code to get the questions and answers.

SCAN ME

If the medication could otherwise be prescribed to the infant for a medical condition, it is generally considered safe for the mother to take while breastfeeding.