Communicating Teratogen Information Effectively: The TIS Perspective

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Disclaimer

I receive $50,000 per year in a subcontract with the Organization of Teratology Information Specialists. The funds originate with HRSA, and are intended for partial support of Mother to Baby Nebraska's educational, research, and service activities.

Mother to Baby/OTIS

Our specialty…

- Access to current and comprehensive data through our listserv, various databases, and literature review
- Ability to synthesize data and highlight the most relevant and important components
- Versed in strategies to effectively convey information to both providers and the general public in a way that it can be used for effective decision making
- Sponsors of national and international research studies to help determine risk of medications used in pregnant and breastfeeding women

OTIS®
Organization of Teratology Information Specialists

MotherToBaby
Medications & More During Pregnancy & Breastfeeding
Ask The Experts

Things to like about the new PLLR….

Elimination of A B C D X codes
- Overly simplistic, easy to misinterpret

Clearer format
- Risk summary, clinical considerations, data

Better data
- Requirement to update information
- Pregnancy Registries
- Extrapolation of animal data to human risk

Expanded information
- Clinical considerations
- Impact on fertility

Areas of concern…

Great wailing and gnashing of teeth over losing A B C D X. Many texts and references persist in using them to easily present and compare pregnancy risk (note 'whack a mole' analogy…you get rid of one and another pops back up).

It takes specialized knowledge and skills to write the PLLR in a clear and effective manner

When weighing liability concerns against balanced presentation of material…liability often wins. It is hard to *prove* safety!

- "published studies have not reported a clear association with metformin and major birth defect or miscarriage risk"
- vs. (most) studies have not reported an association…

Up to Date

Pregnancy Risk Factor C (show table)

Pregnancy Implications

Adverse events have been observed in animal reproduction studies. Escitalopram crosses the placenta and is distributed into the amniotic fluid. An increased risk of teratogenic effects, including cardiovascular defects, may be associated with maternal use of escitalopram or other SSRIs; however, available information is conflicting. Nonteratogenic effects in the newborn following SSRI/SNRI exposure late in the third trimester include respiratory distr cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. Symptoms may be due to the toxicity of the SSRIs/SNRIs or a discontinuation syndrome and may be consistent with serotonin syndrome associated with SSRI treatment. Persistent pulmonary hypertension of the newborn (PPHN) has also been reported with SSRI expo The long-term effects of in utero SSRI exposure on infant development and behavior are not known. Escitalopram is the S-enantiomer of the racemic derivative citalopram; also refer to the Citalopram monograph.

Due to pregnancy-induced physiologic changes, some pharmacokinetic parameters of escitalopram may be altered. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary health care provider, and pediatrician. According to the American Psychiatric Association (APA), the risk: medication treatment should be weighed against other treatment options and untreated depression. For women who discontinue antidepressant medications during pregnancy and who may be at high risk for postpartum depre the medications can be restarted following delivery. Treatment algorithms have been developed by the ACOG and the APA for the management of depression in women prior to conception and during pregnancy.

Pregnant women exposed to antidepressants during pregnancy are encouraged to enroll in the National Pregnancy Registry for Antidepressants (NPRAD). Women 18 to 45 years of age or their health care providers may cont the registry by calling 844-405-6185. Enrollment should be done as early in pregnancy as possible.

Breast-Feeding Considerations

Escitalopram and its metabolite are present in breast milk.

The relative infant dose (RID) of escitalopram is ~3.9% and the RID of the metabolite is ~1.7% when calculated using average milk concentrations and compared to a weight-adjusted maternal dose of 10 to 20 mg/day. In general, breastfeeding is considered acceptable when the RID is <10% (Anderson 2016; Ito 2000); however, some sources note breastfeeding should only be considered if the RID is <5% for psychotropic agents (Larsen 2 The calculations are based on mean milk concentrations of escitalopram 78 ng/mL (reported range: 37 to 168 ng/mL) and demethylescitalopram 27 ng/mL (reported range: 17 to 41 ng/mL). These milk concentrations were obtained following maternal administration of oral escitalopram 10 to 20 mg/day. Mean peak milk concentrations of escitalopram occurred ~5.5 hours after the maternal dose; the mean peak concentration of the metabolite reported at ~4.8 hours (Rampono 2006). However, avoiding breastfeeding during the expected peak concentrations will generally not decrease infant exposure significantly for antidepressants with long half-lives (Berle 20

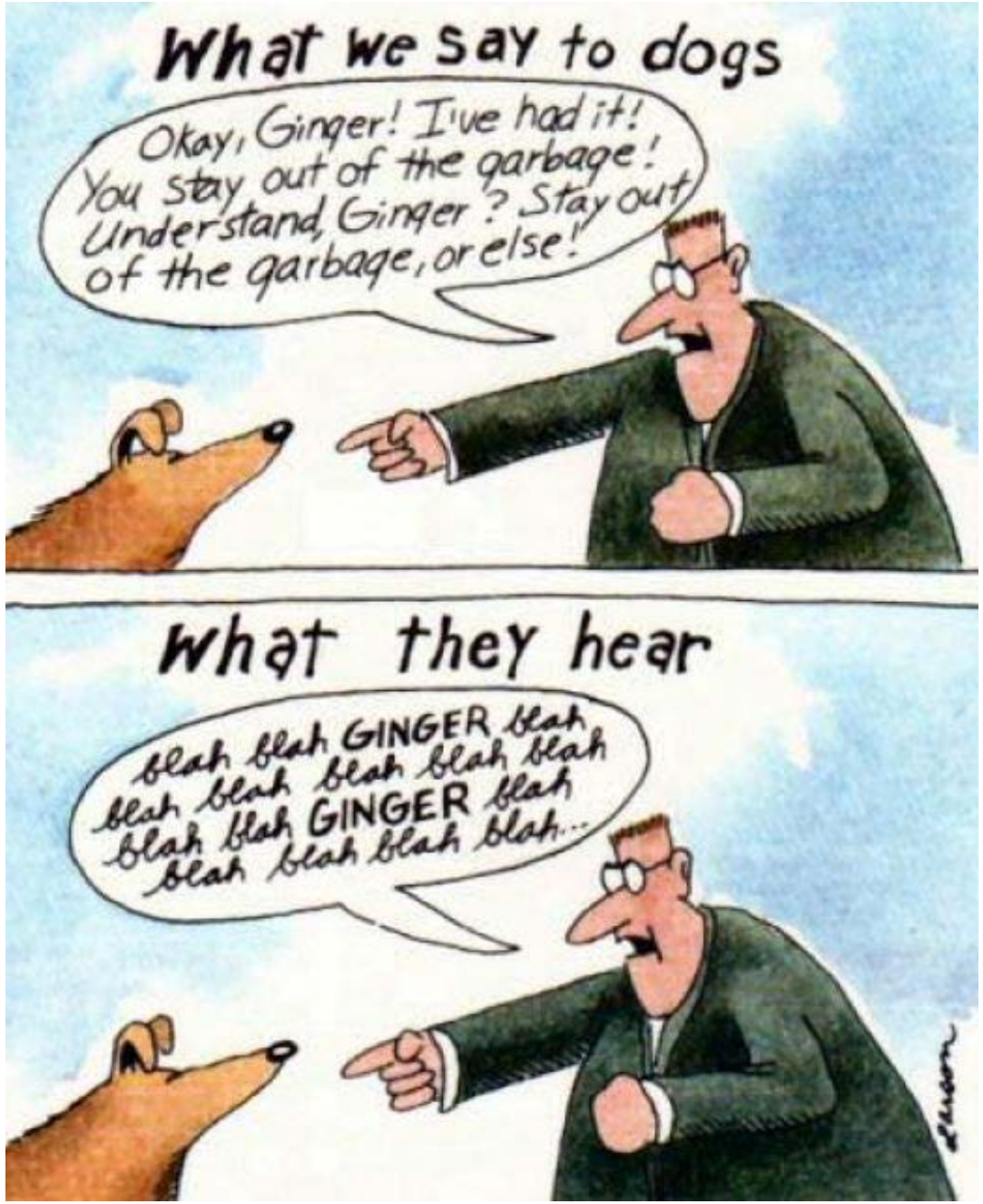
Adverse effects have been reported in breastfeeding infants exposed to SSRIs including escitalopram in some studies (Hale 2010). Infants of mothers using psychotropic medications should be monitored daily for changes sleep, feeding patterns, and behavior (Bauer 2013), as well as infant growth and neurodevelopment (Sachs 2013; Sriraman 2015). Maternal use of an SSRI during pregnancy may cause delayed lactogenesis (Marshall 20

When first initiating an antidepressant in a breastfeeding woman, agents other than escitalopram are preferred. Women successfully treated with escitalopram during pregnancy may continue use while breastfeeding if the

My Pharmacy Visit…patient information

TABLE 4
OTC Antidiarrheal Medications in Pregnancy

Drug name	*FDA pregnancy risk classification by trimester (1st/2nd/3rd)*	*Drug class*	*Crosses placenta?*	*Use in pregnancy*
Kaolin and pectin (Kaopectate)	B/B/B	Antidiarrheal	No	Antidiarrheal of choice (not absorbed)
Bismuth subsalicylate (Pepto Bismol)	C/C/D	Antidiarrheal	Yes	Not recommended (salicylate absorption)
Loperamide (Imodium)	B/B/B	Antidiarrheal	Not known	Probably safe*
Atropine/diphenoxylate (Lomotil)	C/C/C	Antidiarrheal	Not known	Not recommended (adverse animal studies)



Gary Larson, The Far Side

Trailblazers:

Gideon Koren & Motherisk

- Drug labeling and Risk Perceptions of Teratogenicity
- J Clin Pharmacol 40:573-577 (2000)

Janine Polifka

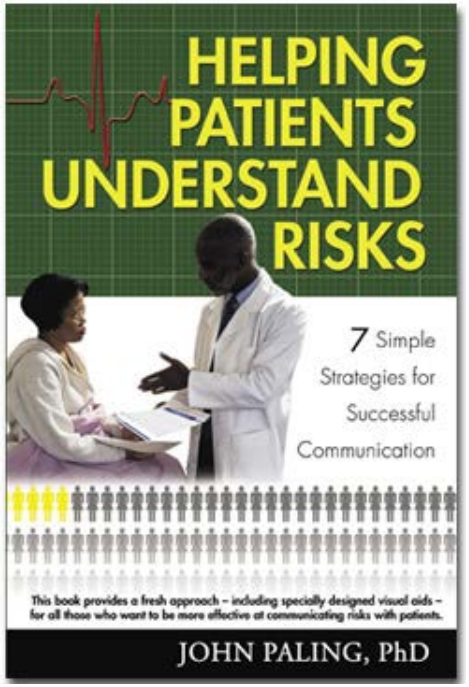
The Art and Science of Teratogen Risk Communication

American Journal of Medical Genetics 157:227-233 (2011)

John Paling

Strategies to help patients understand risks.

BMJ 327:745-748 (2003)



Conundrums

Pregnant women often tend to overestimate the magnitude of teratogenic risk.

Health providers also may have distorted perceptions of risk, even in the presence of evidence-based facts.

Teratogen (and other medical) data may be limited and contradictory.

- There is rarely adequate data on all aspects of reproductive toxicity (ex. adverse behavioral outcomes).

Situations where there is no data or inadequate data predispose to inaccurate and extreme interpretation:

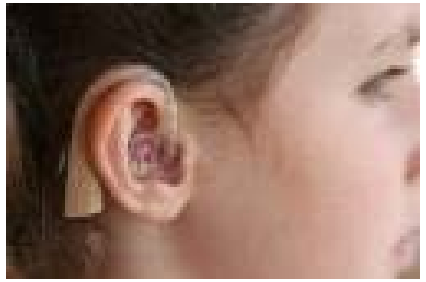
- No data…assume huge risk vs no data…assume no risk

Pole et al. 2000. J Clin Pharmacol 40:573-7.
Ratnapalan et al. 2004. AJR 182:1107-1109

Risk Is More Than Just Probability

Contextual factors:

- Patients attribute higher risk to outcomes perceived to be more severe
- Patients are better able to accept risk if they have control over it or it is voluntary
- Patients find risk more acceptable if it provides them with benefits
- Perception of risk is highly individualized, and it depends on the other risks it is compared to…



Uncertainty

Probabilities by definition involve a degree of uncertainty

It is difficult for people to make complex decisions involving weighing risks/benefits when the risks are uncertain…they prefer 'black and white' situations.

Concept of spectrum of risk may be new to patients and frustrating for health providers (used to safe/not safe)

Patients cope with uncertainty by:

- Denying it exists
- Magnifying it and the accompanying risk

Examples:

- "All or nothing" interpretation of risk
- FDA codes

Numeracy

Findings are often conveyed numerically, a difficult form of information for providers and patients to interpret.

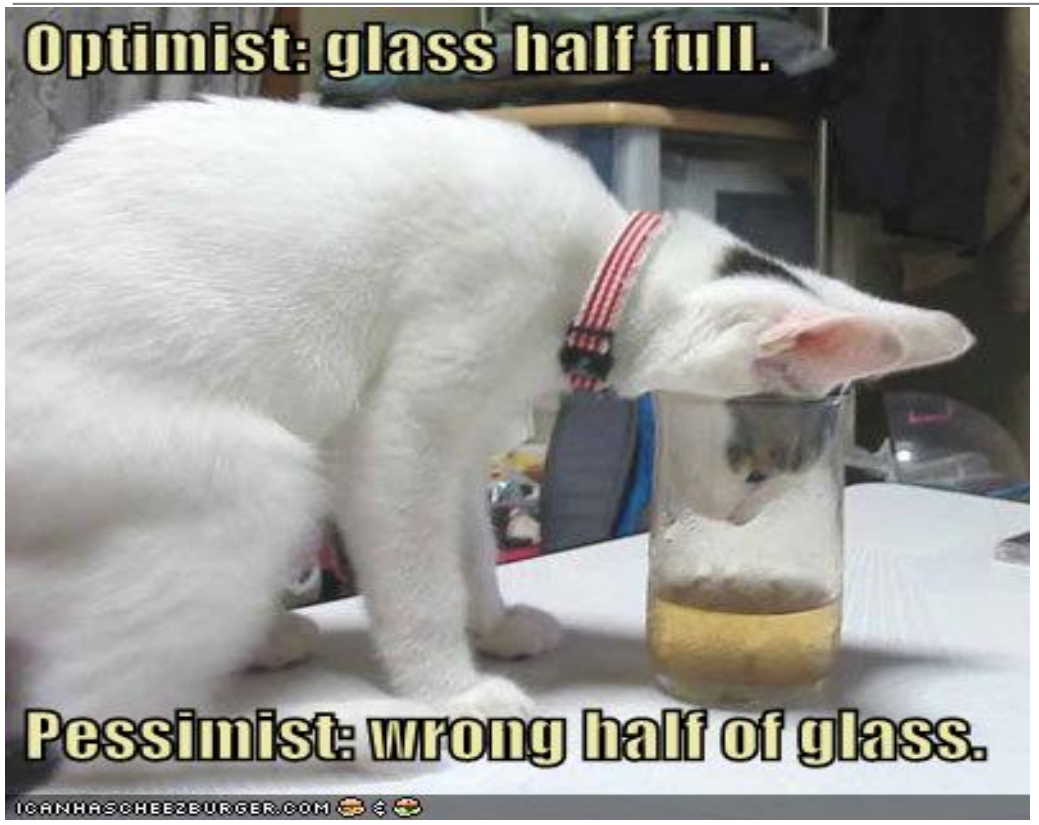
2003 National Assessment of Adult Literacy Survey found that almost half of Americans have difficulties with relatively simple numeric tasks such as calculating; a substantial number of physicians have difficulties understanding and interpreting numeric medical data such as relative risk.

Fewer numeric skills associated with lower comprehension and less use of health information

Less numerate patients likely to make decisions based on emotions, mood states, and trust or distrust in physicians

Less numerate are more susceptible to effects of framing, formatting of probability and risk reduction information, and more trusting of verbal than numerical information

Framing (how the information is worded)



"Loss vs. Gain"

- People respond differently when information is framed positively or negatively
- Ex: 1-3% risk of having a malformed child vs. 97-99% chance of having a normal child

Jasper et al. 2001. Lancet 358:1237-1238.

Relative Risk (RR)…a powerful form of framing

RR is used to compare the risk in two different groups of people:

$$\frac{\text{Incidence in exposed}}{\text{Incidence in unexposed}}$$

RR does not express actual magnitude of risk (depends on prevalence of condition)

A large increase in RR for a rare defect may not mean a large increase in absolute risk

RR may be a useful conceptual tool for scientists, but is generally not appropriate for conveying risks to patients or even providers

AUSTIN ET AL. 2010. J GENET COUNSELING 19:228-234

Absolute risk

Absolute risk is the incidence of disease in a population

Attributable risk is a measure of excess risk over the baseline population

Both are much easier for clinicians and patients to understand, compared to relative risk

Example:

- Baseline risk of NTD's is 1:1000
- Risk in fetuses exposed to Drug X increases to 2:1000
- This is generally perceived as less frightening than saying something is twice as likely to happen (relative risk)

“Risk” as a form of framing

The term “risk” incorporates:

- probability of various outcomes
- the value patients attach to those outcomes

“Risk” carries negative implications compared to “chance” and “probability”

Risk Communication Formats:
Numerical expressions of likelihood

Various presentation formats can affect risk perception, understanding, attitude and behavior

Many people have a difficult time interpreting numbers as personally relevant information

Frequencies

- People tend to rely on numerator and ignore denominator
- 1300/10,000 is perceived to be higher than 26/100

Percentages

- very confusing, especially when used in terms of relative risk

Risk Communication Formats:
Verbal expressions of likelihood

Examples:

- Low risk/High risk
- "People may occasionally experience"

Descriptive terms reflect the speaker's perspective; patient understands risks to be of a totally different order of magnitude

In one study, subjects' perception of "likely" included probabilities ranging from 0.5 to 0.99

In another study, subjects systematically overestimated likelihood of low probability events when given a verbal expression like "low risk"

AUSTIN ET AL. 2010. J GENET COUNSELING 19:228-234
PALING J. 2003. BMJ 327:745-748.

Effective ways to present probability

Use the same denominator in probability information throughout the risk message so patients who neglect the denominator can still compare probability information

- Ex: Comparing 40/1000 and 5/1000 is easier than 1/25 and 1/200

Consider using natural numbers rather than percentages and ratios

- " If there were 100 people in a room with the same chance you have, 5 of them would have a baby with a birth defect"

Decimals are difficult to understand, and should be avoided when possible (ex: likelihood is .05).

Results are mixed about whether percentage (20%) or frequency (20 out of 100) formats promote the greatest understanding

Relative risks are easily misinterpreted and can be mistaken for absolute risk. If necessary to quote relative risk, always include baseline rates of particular adverse outcome.

Effective ways to present probability

Use verbal expressions of probability carefully

- It is difficult to develop verbal expressions that all patients interpret the same way

Use numerical probabilities as a basis for providing risk information, but use verbal qualifiers to place risk in the context of other life events

VISSCHERS ET AL. 2000 RISK ANALYSIS 29:267-287.

Effective ways to present probability

Frame probability in a variety of ways and compare it to the baseline risk for birth defects or other adverse outcomes:

- "Everyone has a background risk for birth defects of 3/100. Your 1/100 risk for baby with a heart defect because of your medication makes your risk 4/100 (or to say it differently, you have a 96/100 chance of having a healthy baby)"

AUSTIN ET AL. 2010. J GENET COUNSELING 19:228-234

Facilitating Decision Making

Use the term ‘chance’ instead of ‘risk’ because chance connotes less of a value judgment of good or bad outcome

Provide numbers in different formats

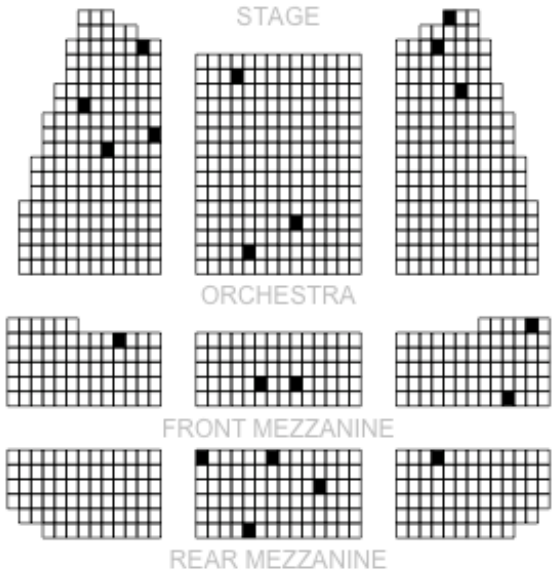
- Ex: use both percentage and ratio (25% or 1 in 4)

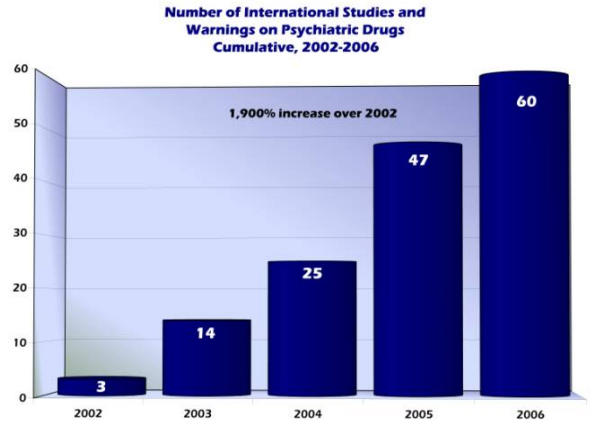
Effective ways to present probability

Offer visual aids such as pie charts, graphs, pictograms, or risk ladders to enhance understanding of probability information

Use care that visual aids do not introduce another form of bias

- when compared to numerical information, graphs are more likely to draw attention to harm
- Pictograms can be helpful, but lead to overestimation of probability (example: 20 out of 1000 risk (2%)





VISSCHERS ET AL. 2000 RISK ANALYSIS 29:267-287.

ERIK RIFKIN AND EDWARD BOUWER'S THE ILLUSION OF CERTAINTY: HEALTH BENEFITS AND RISKS

Risk and Benefit Considerations

Uncontrolled Depression

Maternal:

- Misery
- impaired relations with family
- Poor prenatal care
- use of alcohol/tobacco/illicit drugs

Baby and pregnancy:

- Miscarriage
- Preeclampsia
- Preterm delivery
- Low birthweight

Medication Risks

Baby and pregnancy:

- possible small increase in risk for birth defects (especially heart)
- Possible increase in risk for neurocognitive problems—ADHD, autism, psychiatric illness, delays
- Preterm Delivery
- Persistent Pulmonary Hypertension
- Neonatal Abstinence Syndrome

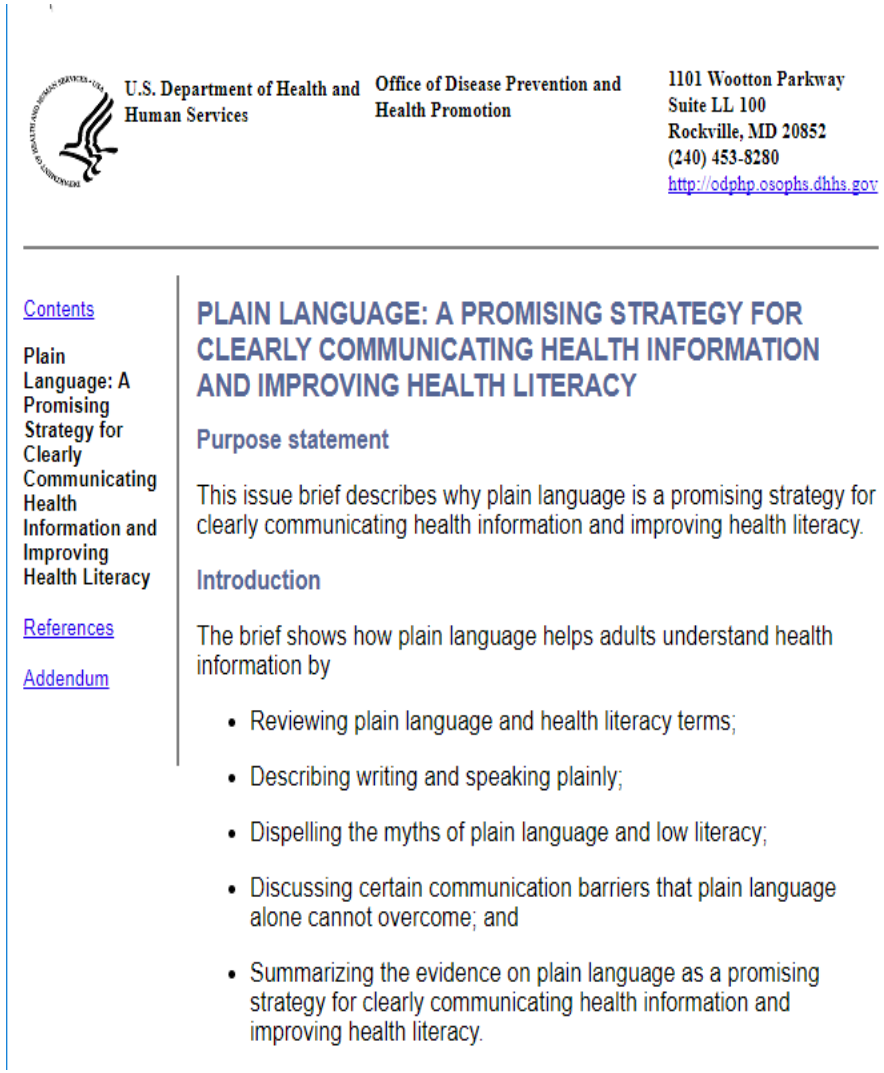
Avoid Medication

Consider Medication

Plain Language

Key elements:

- Organize information so that the most important action points come first
- Break complex information into understandable chunks
- Use simple language to define technical terms; use short sentences and active voice when possible
- Provide ample white space so pages are easy to read
- Plain language may be more persuasive when enhanced by graphics and other visuals
- Specifics depend on information needs of the audience so it is critical to test materials with intended audience



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Contents

Plain Language: A Promising Strategy for Clearly Communicating Health Information and Improving Health Literacy

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Addendum

PLAIN LANGUAGE: A PROMISING STRATEGY FOR CLEARLY COMMUNICATING HEALTH INFORMATION AND IMPROVING HEALTH LITERACY

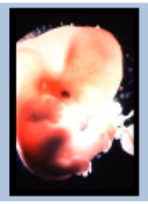
Purpose statement

This issue brief describes why plain language is a promising strategy for clearly communicating health information and improving health literacy.

Introduction

The brief shows how plain language helps adults understand health information by

- Reviewing plain language and health literacy terms;
- Describing writing and speaking plainly;
- Dispelling the myths of plain language and low literacy;
- Discussing certain communication barriers that plain language alone cannot overcome; and
- Summarizing the evidence on plain language as a promising strategy for clearly communicating health information and improving health literacy.



TERIS

The Teratogen Information System

by J.M. Friedman, M.D., Ph.D.
& Janine E. Polifka, Ph.D.

Release 11/28/2016

TERIS Summary

TERIS Agent Number: 6249
Agent Name: **OSELTAMIVIR**

Oseltamivir is a prodrug of oseltamivir carboxylate, a selective, competitive inhibitor of the influenza viral enzyme, neuraminidase. Oseltamivir is administered orally in the prophylaxis and treatment of influenza infections.

Magnitude of Teratogenic Risk to Child Born After Exposure During Gestation: UNDETERMINED

Quality and Quantity of Data on Which Risk Estimate is Based: LIMITED

Comments: A SMALL RISK CANNOT BE EXCLUDED, BUT A HIGH RISK OF CONGENITAL ANOMALIES IN THE CHILDREN OF WOMEN TREATED WITH OSELTAMIVIR DURING PREGNANCY IS UNLIKELY.

Summary of Teratology Studies:

One (1.2%) of 86 infants born to mothers who took oseltamivir during the first trimester of pregnancy was reported to have a major malformation (a ventricular septal defect) in a series collected through two Japanese teratogen information services among 18 newborn infants whose mothers had been treated with oseltamivir during the first trimester of pregnancy in a retrospective record review (Greer et al., 2010). No major malformations were observed among 115 infants whose mothers rec of minor malformations among these infants was no higher than expected.

Congenital anomalies were observed in seven of 26 fetuses or infants of mothers who had been treated with oseltamivir during the first trimester of pregnancy and were voluntarily reported to the pharmaceutical manufacturer (Donner et al., 2010). four instances. Two of the three infants who were exposed during the relevant critical period of embryonic development had ventricular septal defects; the third infant had anophthalmia. These data are very difficult to interpret because of the likelih

No teratogenic effect is said to have occurred when pregnant rats were treated with 250 times the usual human dose of oseltamivir (Donner et al., 2010). Fetal malformations were not increased but embryonic death was frequent when rabbits were pregnancy; this treatment also caused maternal toxicity (Donner et al., 2010).

Agent Detail

TAMIFLU

Print Summary View Plain Text

Agent Number	4141
CAS Number	196618-13-0
Last Updated	08/26/2017

Agent Summary

Quick take: Based on experimental animal studies, oseltamivir therapy during pregnancy is not expected to increase the risk of congenital anomalies.

LACTMED: OSELTAMIVIR CASRN: 196618-13-0 This record appears in multiple databases.

View record in another database: LACTMED | Download this Record | Print | Select Record | My List | Permalink

Recent related PubMed toxicology articles

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Show Selected Items Clear Expand all Collapse all

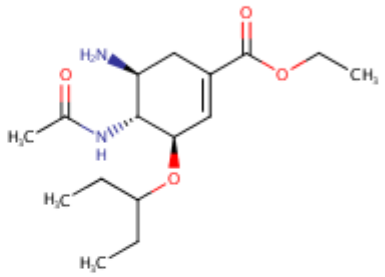
- Closest Match to Search Terms
- Full Record
- Drug Levels and Effects
- Substance Identification
- Administrative Information

Show Selected Items Clear

CLICK TO HIDE

Oseltamivir

CASRN: 196618-13-0



FULL RECORD DISPLAY

Displays all fields in the record.

For other data, click on the Table of Contents

Drug Levels and Effects:

Summary of Use during Lactation:

Limited data indicate that oseltamivir and its active metabolite are poorly excreted into breastmilk. Maternal dosages of 150 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months. Infants over 1 year of age can receive oseltamivir directly in doses much larger than those in breastmilk.

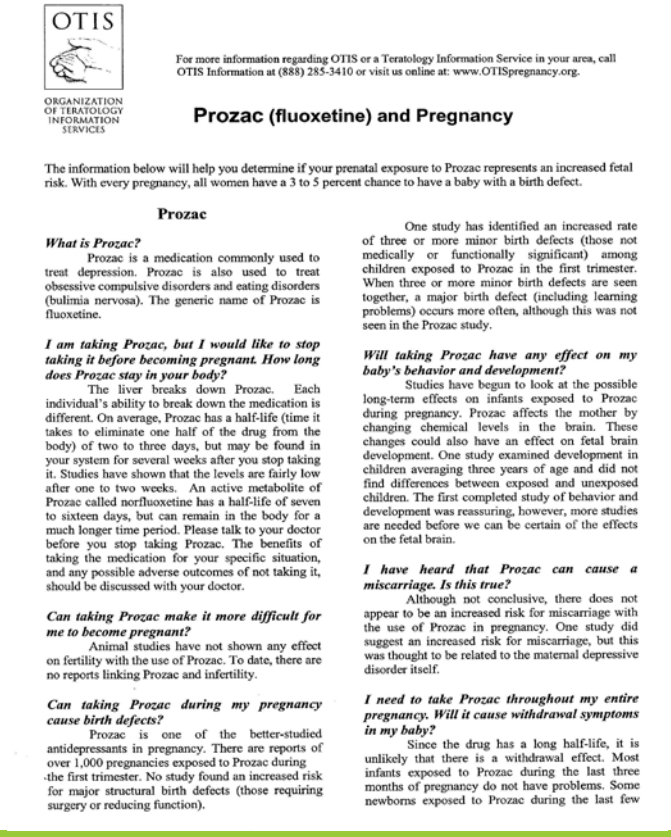
MotherToBaby

Medications & More During Pregnancy & Breastfeeding

Ask The Experts

A service of the Organization of Teratology Information Specialists

- www.mothertobaby.org
- National phone number: (866) 626-6847
  - option for Spanish speaking TIS counselor
- NE-TIS (402)-559-5071



OTIS

ORGANIZATION OF TERATOLOGY INFORMATION SERVICES

For more information regarding OTIS or a Teratology Information Service in your area, call OTIS Information at (888) 285-3410 or visit us online at: www.OTISpregnancy.org.

Prozac (fluoxetine) and Pregnancy

The information below will help you determine if your prenatal exposure to Prozac represents an increased fetal risk. With every pregnancy, all women have a 3 to 5 percent chance to have a baby with a birth defect.

Prozac

What is Prozac?

Prozac is a medication commonly used to treat depression. Prozac is also used to treat obsessive compulsive disorders and eating disorders (bulimia nervosa). The generic name of Prozac is fluoxetine.

I am taking Prozac, but I would like to stop taking it before becoming pregnant. How long does Prozac stay in your body?

The liver breaks down Prozac. Each individual's ability to break down the medication is different. On average, Prozac has a half-life (time it takes to eliminate one half of the drug from the body) of two to three days, but may be found in your system for several weeks after you stop taking it. Studies have shown that the levels are fairly low after one to two weeks. An active metabolite of Prozac called norfluoxetine has a half-life of seven to sixteen days, but can remain in the body for a much longer time period. Please talk to your doctor before you stop taking Prozac. The benefits of taking the medication for your specific situation, and any possible adverse outcomes of not taking it, should be discussed with your doctor.

Can taking Prozac make it more difficult for me to become pregnant?

Animal studies have not shown any effect on fertility with the use of Prozac. To date, there are no reports linking Prozac and infertility.

Can taking Prozac during my pregnancy cause birth defects?

Prozac is one of the better-studied antidepressants in pregnancy. There are reports of over 1,000 pregnancies exposed to Prozac during the first trimester. No study found an increased risk for major structural birth defects (those requiring surgery or reducing function).

One study has identified an increased rate of three or more minor birth defects (those not medically or functionally significant) among children exposed to Prozac in the first trimester. When three or more minor birth defects are seen together, a major birth defect (including learning problems) occurs more often, although this was not seen in the Prozac study.

Will taking Prozac have any effect on my baby's behavior and development?

Studies have begun to look at the possible long-term effects on infants exposed to Prozac during pregnancy. Prozac affects the mother by changing chemical levels in the brain. These changes could also have an effect on fetal brain development. One study examined development in children averaging three years of age and did not find differences between exposed and unexposed children. The first completed study of behavior and development was reassuring, however, more studies are needed before we can be certain of the effects on the fetal brain.

I have heard that Prozac can cause a miscarriage. Is this true?

Although not conclusive, there does not appear to be an increased risk for miscarriage with the use of Prozac in pregnancy. One study did suggest an increased risk for miscarriage, but this was thought to be related to the maternal depressive disorder itself.

I need to take Prozac throughout my entire pregnancy. Will it cause withdrawal symptoms in my baby?

Since the drug has a long half-life, it is unlikely that there is a withdrawal effect. Most infants exposed to Prozac during the last three months of pregnancy do not have problems. Some newborns exposed to Prozac during the last few