

FDA Review of Rx to OTC Consumer Studies involving Adolescents

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Outline

- 1). Introduction**
- 2). FDA Consumer Studies for Rx to OTC switches involving adolescents**
 - Plan B (Levonorgestrel)**
 - Alli (Orlistat)**
- 3). Points to Consider**
- 4). Research issues**

Introduction

- **Over-the-counter (OTC) drug products are those drugs that are available to consumers without a prescription**
- **Numerous therapeutic categories of OTC drugs**
- **Current health climate  in self-medication; adolescents may use more OTC drugs **increased interest****
- **Literature reports suggest that adolescent use of OTC medications increases with age, starts around age 11-12, girls > boys (eg., analgesics)**
- **Limited information regarding magnitude and patterns of use**

Introduction (cont'd)

- **Adolescent decision making skills and risk-taking behaviors regarding use of OTC drugs not well studied**
- **Factors influencing use of OTC drugs may include parents, peers, media, social/socio-economic circumstances, etc.**
- **Consumer studies (label comprehension, self-selection, actual use) for Rx to OTC switches often exclude adolescents**
- **Study design challenges & limitations (informed consent/assent, follow-up, dropout, etc) in enrolling adolescents**

Clinical Implications about OTC Drug Use by Adolescents

- Safety concerns, overdose
- Adolescents may be less aware than adults about toxicities of OTC drugs
- Clinical diagnosis may be confounded by overlooking OTC medications (adolescents may not be as forthcoming as adults about use of OTC drugs)

How do adolescents compare to adults in above respects ?

Correct use of OTC drugs in adolescence → responsible use in adulthood; positive impact

New Drug Application (NDA) Process - Rx to OTC

Considerations for Rx to OTC switch

- Can the condition be adequately self-recognized?**
- Can the condition be successfully self-treated?**
- Is the product safe and effective during consumer use?**

Switch candidate

- Acceptable margin of safety based on prior Rx marketing experience, adequate labeling (OTC labels generally targeted to 8th grade literacy levels)**
- Self-treatment & self-monitoring with minimal physician supervision**
- Benefits outweigh risks**

FDA Rx to OTC Switch Consumer Studies involving Adolescents

#	Drug	Studies
1.	Plan B (Levonorgestrel)	- Label Comprehension (2003) - Actual Use (2003)
2.	Alli (Orlistat)	- Self Selection (2005)

Plan B

(levonorgestrel 0.75 mg)

- **Plan B (levonorgestrel) 0.75 mg tablet, is a progestin-only emergency contraceptive**
- **Available as a 2-tablet (two doses 12 hours apart) package**
- **Approved for emergency contraception**
 - **1999 for Rx use**
 - **2006 for OTC use in women 18 years and older, but retained Rx use for 17 years and younger**
- **Label Comprehension (LC) and Actual Use (AU) studies conducted as part of the Rx to OTC switch process (2003)**

Plan B Label Comprehension Study Design

- Purpose of study was to evaluate comprehension of a prototype OTC package label for Plan B emergency contraceptive (EC) pills
- Communication objectives tested:
 - Indication
 - Back-up method (not regular contraception)
 - Does not prevent sexually transmitted diseases or HIV
 - 1st pill to be taken as soon as possible after intercourse; 1st pill to be taken within 72 hours after intercourse; 2nd pill to be taken 12 hours after first
 - Seek medical help for severe abdominal pain
 - Not to be used by pregnant women, those with unexplained vaginal bleeding, or allergy to ingredients
 - Side-effects

Plan B Label Comprehension Study Design

N = 656 females, age 12 – 50 years

Age Range (years)	%
12-16	12%
17-25	54%
26-50	34%

- **139/395 (35%) subjects tested in lower literacy group on REALM (only on subjects \geq 18 years and not graduated from college). Twenty-eight subjects aged 17 or younger had not been past 8th grade in school**
- **Interviews - in shopping malls (89%) & family planning clinics (11%) in 8 US cities. Minors recruited from clinics did not require parental consent to participate**

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* **REALM = Rapid Estimate of Adult Literacy in Medicine**

Plan B Label Comprehension Study Design

- **Participants used Plan B package and label to answer questions**
- **Questionnaires included multiple-choice & open-ended questions, including hypothetical scenarios**
- **Separate questionnaire about sexual activity presented at the end**
- **Results for the total sample were provided for each question**
- **Results for each communication objective were also provided based on subgroups - literacy, age, race, interview location, income, previous sexual experience, experience using emergency contraception pills, etc.**

Plan B Label Comprehension Study

Key Results by Age

Correct Responses

#	Key Communication Objectives	Age 12-16 n = 76 (%)	Age 17 – 25 n = 355 (%)	Age 26-50 n = 255 (%)
1.	Prevention of pregnancy after unprotected sex	86%	93%	95%
2.	Plan B not for routine use	57%	67%	71%
3.	1 st pill within 72 hours of intercourse	77%	86%	87%
4.	2 nd pill to be taken 12 hours after 1st	77%	90%	82%
5.	Does not prevent STD/HIV	93%	96%	92%
6.	Side effects include nausea & vomiting	90%	93%	84%

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Plan B Label Comprehension Study

Key Results by Literacy Level

REALM test only performed on ≥ 18 years & not graduated from college

#	Key Communication Objectives	Lower Literate (n=139)	Higher Literate (n=254)	Total (n=393)
1.	Prevention of pregnancy after unprotected sex	84%	96%	92%
2.	Plan B not for routine use	46%	78%	67%
3.	1 st pill within 72 hours of intercourse	71%	90%	83%
4.	2 nd pill to be taken 12 hours after 1st	82%	92%	89%
5.	Does not prevent STD/HIV	84%	99%	93%
6.	Side effects include nausea & vomiting	84%	96%	92%
7.	Not to be used by women with unexplained vaginal bleeding	69%	81%	77%

Plan B Label Comprehension Study Results

Study Limitations

- **Small number of adolescents enrolled**
- **Literacy testing**
 - not performed on all participants,
 - only on those ≥ 18 years and not graduated from college
- **Answers to questions included yes/no and correct/incorrect variety**
 - 50% correct by chance alone
 - probing questions not asked as follow-up
- **Women with prior experience with emergency contraception not excluded**

Plan B Actual Use Study (2003)

- **Pivotal, open-label, multi-center trial**
 - **5 family planning clinics (94%) and 5 pharmacy stores (6%) in US;**
 - **sites chosen to avoid recruitment difficulties in public places**
- **Label improvements included emphasizing (bolding) timing of pills, etc**
- **Demographically diverse population**
- **Age – no restriction (except Phoenix and Arizona, where 15 and younger were excluded because parental consent was required)**
- **N = 540 subjects (14 – 44 years) took Plan B**
 - **91% were 18 to 44 years**
 - **5% were 17 years**
 - **4% were 14 to 16 years**

Plan B OTC Label (Drug Facts)

Drug Facts

<i>Active ingredient (in each tablet)</i>	<i>Purpose</i>
Levonorgestrel 0.75mg.....	Emergency contraceptive

Use reduces chance of pregnancy after unprotected sex (if a contraceptive failed or if you did not use birth control)

Warnings

Allergy alert: Do not use if you have ever had an allergic reaction to levonorgestrel

Sexually transmitted diseases (STDs) alert: This product does **not** protect against HIV/AIDS or other STDs

Do not use

- if you are already pregnant (because it will not work)
- for regular birth control

When using this product you may have

- | | | |
|---------------------|---------------|----------------|
| ■ nausea | ■ vomiting | ■ stomach pain |
| ■ tiredness | ■ diarrhea | ■ dizziness |
| ■ menstrual changes | ■ breast pain | ■ headache |

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control center right away.

Directions

- women 18 years of age and over:
 - **take the first tablet as soon as possible but no later than 72 hours (3 days) after unprotected sex. The sooner you take the first tablet, the more effective it will be.**

Plan B Actual Use Study Design

- **Objective – Estimate frequency of contraindicated & incorrect use of Plan B in simulated OTC environment**
- **Participants learned about Plan B by reading product label & self-selected. No education provided about Plan B or other forms of contraception.**
- **Follow-up at 1 and 4 weeks later by phone or at study site**

Educational level (Literacy testing not done)

- ***14-16 years group* - 3% of subjects had \leq 8th grade education; 97% were in 9th-11th grade**
- ***\geq 17 years group* - 9% had completed 9th-11th grade; 14% were high school graduates; 77% had completed some form of college**

Plan B Actual Use Study Results

- Overall, reasons to use Plan B were similar among different ages, races, ethnicity, educational levels & ever/never EC use experience
- Percentage of contraindicated use was 4.4% (pregnancy, unexplained vaginal bleeding, allergy)
- Pregnancy confirmed in 10 participants who took Plan B; pregnancy status of 14 unknown
- No new adverse events observed

Plan B Actual Use Study Results

Reasons to use by Subgroups

Nature of contraception failure	Age (yr)		Education	
	≤ 16 N = 22	≥ 17 N = 518	< HS N = 64	> HS N = 476
Condom failure	54.5%	44.8%	46.9%	45.0%
Used no contraception	27.3%	40.2%	28.1%	41.2%
Missed OCPs	9.1%	6.8%	10.9%	6.3%
Withdrawal	9.1%	3.3%	7.8%	2.9%
Other	0.0%	3.1%	3.1%	2.9%
Missing	0.0%	0.6%	0.0%	0.6%

Plan B Actual Use Study Results

Timing of Doses

Majority of patients took the first pill within 72 hours (per label) and the second pill by 12 hours after the first (per label); no age difference

	AGE (YRS)	
	≤ 16 yrs (N=22)	≥ 17 yrs (N=518)
Timing for first pill		
< 72 hours	86.4%	92.7%
< 72 hours	0%	1.9%
Missing data	13.6%	5.4%
Interval between first & second pill		
At 12 hours	81.8%	71.2%
</> 12 hours	13.6%	25.7%
Missing data	4.5%	3.1%

Plan B Actual Use Study Results

Correct Timing Data of Both Pills

No difference in timing in taking both pills between ages 14-17 & 18-44; younger population had slightly better compliance rates for timing compared to adults

Subject Age (yrs)	Plan B Users N (%)	Correct Timing Both Pills (%)
14 - 16	22 (4%)	77%
14 - 17	46 (9%)	75%
18 - 44	494 (91%)	72%
Total	540 (100%)	72%

Plan B Actual Use Study Results

Compliance of Follow-Up Contacts

Subjects ≤ 16 years & those with less than high school (HS) education were less compliant

# of F/U visits	Age (yrs)		Education levels	
	14-16	17-44	< HS	\geq HS
	N = 29	N = 556	N = 78	N = 507
0	24.1%	6.5%	19.2%	5.5%
1	20.7%	4.1%	11.5%	3.9%
2	55.2%	87.2%	66.7%	88.6%
≥ 3	0	2.2	2.6	2.0

Plan B Actual Use Study Results

Contraceptive Behavior Data

Subjects aged 14-16 and 14-17 years had no more adverse contraceptive behaviors than the 18 - 44 years age group following use of Plan B

Age (yrs)	Contraceptive Behavior Changes (%)			
	More effective	Less effective	Condom use	No condom use
14 – 16	29	0	0	0
14 – 17	27	4	0	4
18- 44	10	9	11	5
Total	11	8	10	5

Plan B Actual Use Study Results

Limitations

Study Limitations

- **Small numbers of teenagers enrolled; 5% of population was 17 years and only 4% was 14 to 16 years**
- **Follow-up only 1 month. Unable to assess recurrent use of Plan B**
- **Enrollment in 'pre-selected' setting because teenagers came to clinic seeking contraception**

Outcome

Plan B retained Rx status for < 17 years. Sample size of teenagers 14 to 16 years too small to draw conclusions.

Alli (Orlistat 60 mg capsule)

Adolescent Self-Selection Study

- Alli (orlistat) – weight loss drug (pancreatic lipase inhibitor) that acts by inhibiting gastrointestinal uptake of ingested fat
- Approved OTC (60 mg) for overweight adults 18 years and older in 2007; Rx (120 mg) approval 1999
- Consumer studies (label comprehension, actual use) conducted for Rx to OTC switch
- Adolescent self-selection study (2005) conducted to determine if teenagers 14 to 17 years of age would chose not to use orlistat based on label directions
- OTC label indication- ‘For weight loss in overweight adults, 18 years and older, when used with a reduced-calorie and low-fat diet’

Alli OTC Label (Drug Facts)

Drug Facts

Active ingredient (in each sealed capsule)	Purpose
Orlistat 60 mg.....	Weight loss aid

Use

- for weight loss in overweight adults, 18 years and older, when used along with a reduced-calorie and low-fat diet

Warnings

Organ transplant alert:

- do not use if you have had an organ transplant. Orlistat interferes with the medicines used to prevent transplant rejection.

Allergy alert:

- do not use if you are allergic to any of the ingredients in orlistat capsules

Do not use

- if you are taking cyclosporine
- if you have been diagnosed with problems absorbing food
- if you are not overweight

Alli Adolescent Self-Selection Study Design

- **Alli self-selection study included only adolescents**
- **N = 147; male (44%) & female (56%) teenagers aged 14 to 17 years interested in losing weight**
- **'All-comers' interested in losing weight recruited using flyers - 8 geographically dispersed sites**
- **Screening interview- only teens 14 to 17 years continued in study; product package and label reviewed to make self-selection decisions**
- **16% of subjects were overweight; 20% at risk of being overweight**

Alli Adolescent Self-Selection Study - Demographic Profile

N = 147

Age (n)	Percentage
17 years (48)	33%
16 years (44)	30%
15 years (30)	20%
14 years (25)	17%

Race: Caucasian 81%; African American 9%; Native American 2%; Asian 3%; Other 4%

Literacy: (8th grade reading level) using Adult REALM test – Literate 63%; Low literate 37%

Alli Self-Selection Study Results

Correct & Incorrect Decisions

- Correct decision – 59% (87/147) said product not appropriate for them
 - Due to their age 68% (60/87)
 - Not overweight 18% (16/87)
 - Pill inappropriate 8% (7/87)
 - Other reasons 5% (4/87)
- Incorrect decision - 41% (60/147) said product appropriate for them
 - Wanted to lose weight 68% (41/60)
 - Believed met requirements for use (missed age direction) 20% (12/60)
 - Liked the program 5% (3/60)
 - Felt it was safe to use 5% (3/60)
 - Thought they could use as preventative 2% (1/60)

Alli Self-Selection Study Results

Purchase Decisions

- **Incorrect self-selectors** (60/147 subjects had indicated orlistat was appropriate)
 - 43 of 60 (72%) indicated they would buy the product, but...
 - 17 of 60 (28%) indicated they would buy the product based on price of \$54.99 for a 30-day supply
- **Overall population** (n = 147)
 - 46 of 147 (31%) subjects indicated they would buy the product, but...
 - 19 of 147 (13%) indicated they would buy the product based on a price of \$54.99 for 30-day supply

Alli Self-Selection Study Results & Body Mass Indices (BMI)

Comparative analysis performed to cross-reference BMIs of enrolled teens with response to the Question: ‘Based on information provided on the package label, is this product appropriate for you to use or not?’

Results – BMI results indicated 16% were overweight and 20% were at risk of being overweight; 63% were normal weight and 1% were underweight.

Incorrect self-selection and purchase decisions were more likely to be made by those overweight and at risk of being overweight (60%), compared to those underweight or normal (29%)

Alli Adolescent Self-Selection Study Results

Conclusions:

- 41% (60/147) of teenagers incorrectly self-selected
- Primary motivation for incorrectly self-selecting was urge to lose weight (68%)
- Teens overweight or at risk of being overweight were more inclined to incorrectly self-select & purchase orlistat
- Price of the product influenced decision to buy in the inappropriate self-selector group (? funds)

Consumer studies involving adolescents – Points to consider

- Primary motivation to self-select an OTC drug in adolescent age groups appears to be the underlying disease process
- Purchase decisions by adolescents may be independent of self-selection and may be dependent on available funds & other influences
- Adolescents may have less comprehension than adults on some communication objectives (eg., Plan B)
- Follow-up not optimal and higher drop-out rates for adolescents (not atypical for this age group)
- *However*, number of FDA studies and patients enrolled inadequate to allow determination of adolescent comprehension and decision making regarding use of OTC drugs

Consumer studies involving adolescents – Points to consider

- **In future, there may be more OTC drugs that adolescents may use**
- **Number of adolescents using OTC drugs may increase**
- **More OTC consumer studies enrolling adolescents**
- **Challenges with enrolling adolescents age groups – recruitment difficulties, informed consent, follow-up, drop-outs**
- **Literacy assessment using appropriate tools - REALM/Teen* test**
- **OTC labels targeted towards 8th grade literacy**

***Development & Validation of the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) – Pediatrics 2006;118;e1707- e1714**

Potential Research Topics for Adolescents & OTC Medications

- Age at which self administration of OTC medications starts and patterns of use
- Knowledge of potential toxicities of OTC drugs
- Decision making about self-selection and purchase
- Identifying relevant situations where differences in information processing & decision making between adolescents & adults warrant consumer studies (label comprehension, actual use) in adolescent age groups
- Impact of low literacy on health care? Early interventions helpful?
- Methods of overcoming study design challenges involving adolescents (e.g., enrollment, consent, follow-up)
- Post-marketing validation of Rx to OTC switch consumer studies ?