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Key Words
Direct-to-consumer (DTC)
advertising;
Risk information;
Communication;
Highlight section;
Brief Summary

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This study was performed in
the United States and
was sponsored by
Eli Lilly and Company.

A New Model for Communicating Risk Information in Direct-to-Consumer Print Advertisements

Direct-to-consumer (DTC) pharmaceutical print ads are required by law to carry a "fair balance" of risks and benefits. There are little quantitative data on the effectiveness of risk communication to the consumer. A questionnaire-based method was used to compare consumer reactions to DTC print advertisements that varied in the amount and format of health risk information presented. The highest-scoring

ads contained risk information in a prominent risk window. As the number of side effects listed (4, 8, or 12) increased, more consumers recalled no side effects correctly (37%, 45%, and 53%, respectively). On the basis of these results, communication of risk information to consumers could be improved by highlighting risks using a window format, and limiting the number of common side effects listed.

INTRODUCTION

Direct-to-consumer (DTC) drug advertising and its role in educating the consumer and improving public health continue to be heavily debated, particularly in light of concerns over the safety of COX-2 inhibitors. In addition to describing the benefits of treatment, a fundamental responsibility of DTC advertising is to convey the risks associated with a drug to the consumer. This will help consumers decide whether to talk to a health care professional about the drug and may reduce unnecessary visits to and unreasonable requests of the health care professional.

The Food and Drug Administration (FDA) requires DTC print ads to carry a "fair balance" of information about benefits and risks. Currently, some risk information is almost always presented on the front (or first) page with promotional text. On the back (or second) page of the ad, the requirement of more comprehensive risk information is usually fulfilled through use of the complete risk-related sections of the FDA-approved professional labeling for the advertised drug (the Brief Summary). The effectiveness of such a format in delivering risk information that is both understood and remembered by the reader has been questioned (1).

Since DTC ads are targeted to the consumer, it is *their* perception and understanding of the ad that is the crux of an effective ad, and the need

for a more consumer-friendly approach is recognized by regulators, medical professionals, and the public (2,3). In January 2004, the FDA proposed recommendations for more effective disclosure of risk information in DTC print ads (2), including the use of consumer-friendly language and a change in format to increase comprehension and retention. Moreover, the agency suggested that omission of information on minor and less common risks may help consumers to focus on the more important risk information. Yet rigorous data to support use of alternate approaches to presentation of risk information are scarce (4,5). Although survey data and opinion research have been published, these efforts were not designed with the intent to improve consumer understanding of health risks associated with drug therapy. In contrast, the current study was performed to generate data to assist FDA regulators and pharmaceutical companies in developing more appropriate ways to present safety information as part of DTC advertising.

The primary aim of this exploratory study was to compare consumers' reactions to a range of pharmaceutical print ads for a single product and disease by varying the amount and format of risk information presented on the front and back pages. Ad layouts considered in this study included the FDA's traditional approach, relying on the Brief Summary, as well as ad layouts incorporating targeted and prominently displayed

risk information. The results of this study provide important information on attributes of a print advertisement that may assist with better communication of risk information to consumers before they decide to initiate discussions with their health care professionals. A related objective was to evaluate how the number of side effects (4, 8, or 12) listed on the front page of the print ad affected the recall of side effects. This is the first study to employ a randomized design with an objective scoring system for ad evaluation to compare specific ads in a controlled viewing environment, rather than to rely on general perceptions of DTC ads.

MATERIAL AND METHODS

This was a randomized study designed to compare the ability of 14 print ad prototypes for the same drug to convey health risk information to readers. In a separate analysis, the effect of number of listed side effects in an ad on recall by the reader was evaluated. Ads were for a fictitious product, Atentin, indicated for the treatment of major depressive disorder, and the ad content was based on an approved label for a marketed compound in the same category.¹

AD PROTOTYPES

For assessment of an ad's ability to convey risk information, 14 ad prototypes of various combinations of one of five front and four back pages (Table 1) were compared. Format AS was chosen for comparison with other ad prototypes since it complies with current FDA requirements and is widely employed with consumers by pharmaceutical companies. Other back pages (P and H) were chosen to reflect alternate approaches postulated by FDA (2). Front pages B and C included risk information in prominent windows, similar to those required for nutritional labeling. Ads without a back page were only evaluated in combination with a front page that contained risk information.

The effect of the number of listed side effects

on recall was also evaluated, using Ad BP (four side effects listed in a window on the front page and in the back-page Patient Package Insert), and modified versions of Ad BP that listed 8 or 12 side effects in the front-page window (BP8 and BP12, respectively).

SAMPLE POPULATION

Electronic invitations were sent to 27,366 adults randomly selected from panels of potential respondents registered with Harris Interactive® (Rochester, NY) and living within the United States. Of these invitees, 2,154 participants aged 18 years and older were enrolled in this study. The study population was stratified to comprise roughly equal numbers of diagnosed (self-reported) depression sufferers ($n = 743$), caregivers (ie, those living with an individual diagnosed with depression) ($n = 648$), and adults in the general population who were neither diagnosed with depression nor caregivers ($n = 763$). To reflect the gender disparity in depression prevalence (6), women were oversampled (60%) in the depression sufferers group.

AD EVALUATION

Data were collected in July 2004, using an Internet-based questionnaire to control ad viewing during the questioning. For any recall questions, participants were not permitted to review the ads before answering.

Assessment of Ad Ability to Convey Health Risk Information. A decision tree process (Figure 1) was developed to identify candidates for effective ads. Each of the 14 ads was initially evaluated on the basis of the reader's opinion of both the effectiveness of the ad in communicating information and the amount of risk information included in the ad, as well as the reader's ability to comprehend information included in the ad (Figure 2). These qualities formed the basis of the primary composite score. Each ad received a primary composite score of 0 to 12. If

¹ This study was conducted before the mandatory requirement by FDA in late 2004 of a warning or boxed warning in the prescribing information of antidepressant medications, describing the increased risk of suicidality in patients being treated with these agents.

Description of the Content of the 14 Prototype Ads.

TABLE 1

Front Page:	Back Page:			
	S: Traditional Brief Summary (Full Page)*	P: Patient Package Insert Q&A Format (Full Page)†	H: Consumer-Friendly Risk Highlights (1/3 Page)‡	a: No Back Page
A: Traditional ad with fair balance in text body (Warnings/CI/4 SE)	AS N = 321, *N = 377	AP N = 106, *N = 85	AH N = 112, *N = 94	
B: Ad with fair balance in risk window (CI/Warnings/4 SE)		BP N = 114, *N = 98	BH N = 117, *N = 123	Ba N = 127, *N = 122
C: Ad with fair balance in risk window (4 SE)		CP N = 121, *N = 130	CH N = 137, *N = 149	Ca N = 100, *N = 98
D: Ad with learned intermediary language in risk window§		DP N = 130, *N = 126	DH N = 107, *N = 83	Da N = 118, *N = 151
E: Ad with no risk information on front page		EP N = 159, *N = 140	EH N = 157, *N = 163	

The number of participants for each ad is shown. Ads in *italics* represent the four most effective ads based on comparison of primary and secondary composite scores and recall of side effects through close-ended questioning. Copies of these ads are shown on pages 121–127. SE, side effects; CI, contraindications; *N, weighted N used for analyses (see text for details).

For all back pages (S, P, and H) the risk section includes side effects, warnings, and contraindications.

*Complete risk-related sections of FDA-approved professional labeling. Most common back-page format in current use and required by FDA regulations and the US Food and Drug Act.

†Based on FDA-approved patient labeling, currently available for some marketed products in lieu of Brief Summary.

‡Consumer-friendly modification of FDA-proposed "Highlights of Prescribing Information" (section of the FDA-approved professional labeling that includes the most important risk information. A possible replacement of Brief Summary). Parallels the new easy-to-read format of drug labeling (Physician Labeling Rule) that the FDA implemented in January 2006.

§Only generic risk information on side effects associated with use of prescription drugs (ie, risk information not specific to Atenolol).

no single ad scored significantly higher than all other ads, further analysis was performed for those ads with primary composite scores that were not statistically different from the highest scoring ad.

For this subsequent analysis, those ads that were indistinguishable on the basis of their primary composite score received a secondary composite score ranging from 0 to 4 based on answers to questions addressing the reader's perception of the ad (Figure 2). If no single ad scored significantly higher than all other remaining ads, those ads with secondary composite scores that were not statistically different from the highest scoring ad were analyzed further.

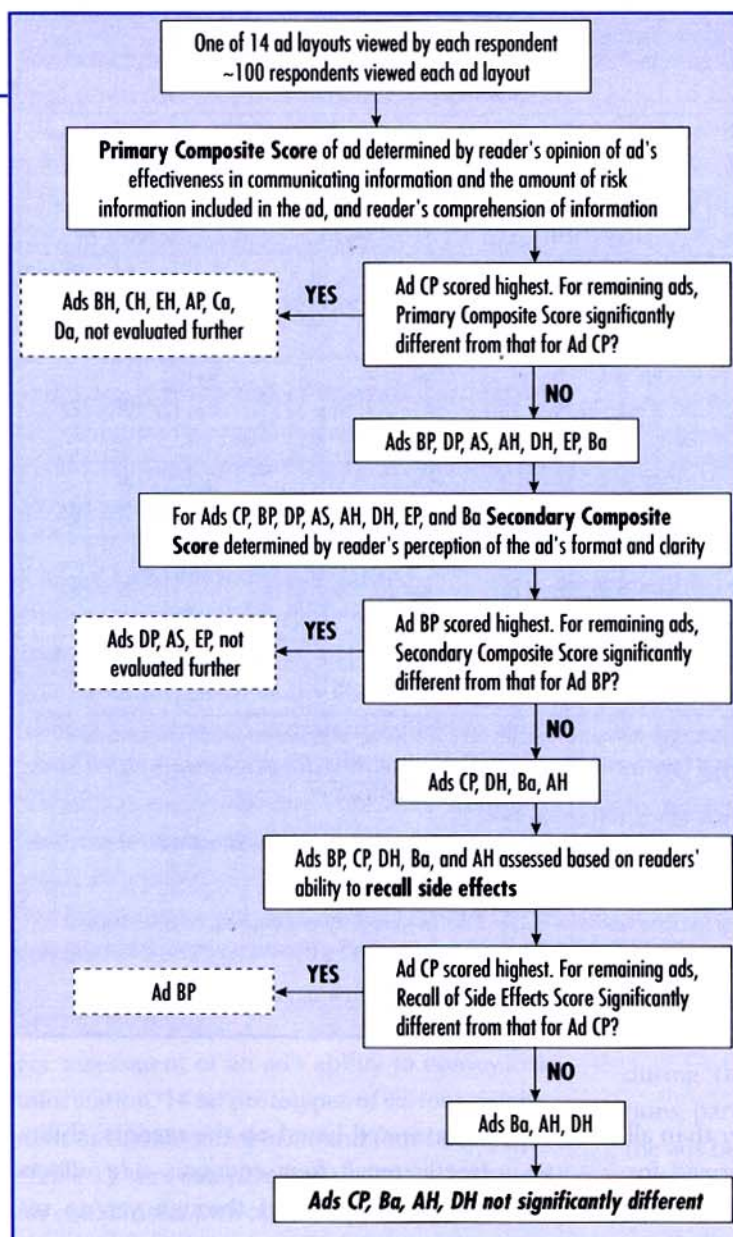
To further differentiate those ads that were indistinguishable on the basis of their primary and secondary composite scores, any remaining

ads were assessed based on the readers' ability to correctly recall four common side effects communicated in the ad through yes/no responses to an eight-item question. Since random guessing would be expected to yield four correct answers, readers who correctly answered zero to four of the eight-part question scored zero, while five to eight correct answers were transformed to a score of 1 to 4. If no single ad scored significantly higher than all other remaining ads, those ads with scores not significantly different from the highest scoring ad were included in further discussion as candidates for effective ads in disclosing health risks associated with the advertised drug.

Effect of Number of Listed Side Effects on Recall of Side Effects. Open-ended question-

FIGURE 1

Decision tree process used to evaluate ad layouts. The progress of each of the 14 ad prototypes through the decision tree is shown.



ing was used to determine the participants' ability to accurately recall side effects from the front or back page where 4 (BP), 8 (BP8), or 12 (BP12) common side effects were listed in the front-page risk window. Other than the number of side effects listed on the front page, ads BP, BP8, and BP12 were identical, even in font size.

STATISTICAL ANALYSIS

A sample size of 100 respondents per ad would provide 91% power to detect a difference of 1 unit on the primary composite score using

analysis of variance (ANOVA) and assuming a common standard deviation of 2 units.

To adjust for possible selection bias introduced through use of a Harris Interactive Internet survey, propensity weighting was applied so that the sample depressed population, and caregiver and general populations mirrored depression sufferers and those not suffering from depression, respectively, within the US population in terms of demographics, attitudes, and behaviors. To calculate weights, a validated method, developed by Harris Interactive and based on

Primary Composite Score**Comprehension True/False**

- Depression is a real illness that can be treated with Atentin
- If you've been feeling sad/irritable for a few days in a row, you probably have depression
- You can buy Atentin without a prescription from a doctor
- Only a doctor can determine if Atentin is right for you
- Atentin does not cause any side effects
- You don't need to tell your doctor about dietary supplements you take before taking Atentin
- Atentin is better than other prescription medications to treat depression
- You should tell your doctor if you are on cholesterol lowering meds before taking Atentin
- Before taking Atentin, you should tell your doctor if you have heart disease
- There are people who have certain medical conditions who should not take Atentin

Effectiveness of Communication 1 (not at all effective)—5 (extremely effective)

- Rate how effective the ad is in providing the information you need to talk to your doctor about Atentin

Amount of Risk Information "not enough," "too much," or "enough"

- Rate the amount of risk information provided in the ad that you need to talk to your doctor about Atentin

Secondary Composite Score**Format/layout 1 (extremely hard), 2, 3, 4, 5 (extremely easy)**

- How easy or hard was it to find what you consider the most important risk information on the front page of this ad?
- back page of this ad?

Clarity of Risk Communication 1 (not at all clear), 2, 3, 4, 5 (extremely clear)

- Rate how clearly the ad communicated what you consider the most important risk information on the front page of this ad?
- back page of this ad?

FIGURE 2

List of those questions used in calculating the primary and secondary composite scores. To calculate the "primary composite score," the responses for each component (comprehension, effectiveness of communication, and amount of risk information) were each transformed to a score of 0 to 4 and then summed. The score assigned for the comprehension component was mapped to 0, 0.8, 1.6, 2.4, 3.2, and 4.0 for 0 to 5, 6, 7, 8, 9, and 10 correct answers, respectively. For questions requiring a response rated 1 to 5, responses of 1, 2, 3, 4, and 5 were assigned scores 0, 1, 2, 3, and 4, respectively. The scores assigned for the amount of risk information component were 0 for "not enough," 2 for "too much," and 4 for "enough." To calculate the "secondary composite score," responses to each of the 4 questions were transformed to a score of 0 to 4 and an average calculated. For each question, responses of 1, 2, 3, 4, and 5 were assigned scores 0, 1, 2, 3, and 4, respectively.

the statistical methodology of Rosenbaum and Rubin (7,8), was employed.

Primary and secondary composite scores and recall of side effects scores were compared between ads using ANOVA incorporating the propensity weights. Where statistically significant differences were evident ($P < .05$), Tukey's multiple comparison procedure was used to identify statistical differences between pairs of ads while maintaining an overall type I error of .05.

To evaluate the consistency of results across consumer groups (depression sufferer, caregiver, or general public), any interaction of primary and secondary scores and recall of side effects with consumer group was identified using propensity-weighted ANOVA, incorporating the effects of ad, subgroup, and interaction between ad and subgroup. Any significant interactions were explored qualitatively.

Differences in the mean number of side effects recalled for BP, BP8, and BP12 were assessed using propensity-weighted ANOVA. The relation-

ship between being unable to accurately recall any side effects correctly and number of side effects listed (4, 8, or 12) was determined using Kendall's tau-c rank correlation coefficient.

RESULTS

Ad layouts were evaluated by 2,154 respondents, comprising depression sufferers, caregivers, and the general population. Table 2 shows the demographics of respondents by subgroup.

The progress of each ad prototype through the decision tree process is shown in Figure 1. Ad CP had the highest mean primary composite score, but ads BP, DP, AS, AH, DH, EP, and Ba did not differ significantly from Ad CP (Figure 3a). These eight ads were thus further analyzed on the basis of format, layout, and clarity of communication, using a secondary composite score.

Ad BP had the highest secondary composite score, but ads CP, DH, Ba, and AH did not differ significantly from Ad BP (Figure 3b). These five ads were further analyzed on the basis of recall

TABLE 2

Demographics of Sample Population, by Population Subgroup and Overall				
	Depression Sufferers (n = 743)	Caregivers (n = 648)	General Population (n = 763)	Overall (N = 2,154)
Male, %	32	56	44	43
Caucasian, %	84	84	71	80
Age ≤ 40 years, %	44	44	50	46
Education				
High school or less, %	35	38	39	37
College degree or higher, %	28	33	26	29
Employed, %	54	74	66	64
Data have been weighted. (See "Statistical Analysis" section.)				

of side effects. Ad CP had the highest score in this case, but this score was not significantly different than those for ads Ba, AH, and DH (Figure 3c). The four ad prototypes that were not significantly different from one other in these prespecified analyses (CP, Ba, AH, and DH) are shown in Figure 4.

There was a significant interaction between ad and subgroup (depression sufferer, caregiver, general population) ($P < .05$). To understand differences between the subgroups, ads were ranked within each subgroup by primary composite, secondary composite, and recall of side effects scores, as well as by the sum of these individual scores. The three highest scoring ads for each score by subgroup and overall are shown in Table 3. The four ad prototypes that were indistinguishable in the prespecified analyses for all respondents (ie, CP, Ba, AH, and DH) all appeared in the three highest-scoring ads in at least one population subgroup (see sum of individual scores). Only Ad CP was in the top 3 highest-scoring ads for the primary composite score and the sum of individual scores across all three subgroups. Ad AS appeared on only one occasion (third highest primary composite score in the general population).

Modified versions of Ad BP were used to evaluate the effect of number of disclosed common side effects (4, 8, or 12) on side effect recall. The mean number of side effects recalled for BP (weighted N [*N] = 98), BP8 (*N = 91), and BP12 (*N = 124) were 1.04, 1.18, and 0.85, re-

spectively, and there were no significant differences between groups ($P = .10$); no specific side effect was consistently recalled by respondents.

The proportions of respondents unable to accurately recall any side effects correctly for BP, BP8, and BP12 were 37%, 45%, and 53%, respectively. These percentages were significantly correlated with number of side effects listed (Kendall's tau-c, .15; $P = .02$).

DISCUSSION

Because no drug is risk free, its value must be considered in terms of its benefits and risks. In this study, we describe an objective method to compare various DTC ad layouts, in an attempt to identify attributes that are more successful in the communication of risk information to the consumer.

Ads were initially evaluated based on readers' opinions of the ad's ability to provide useful information to readers before they talked with their doctors, readers' opinions of the amount of risk information presented, and readers' comprehension of the ad. Assessment of reader perception of ad format and clarity, as well as recall of side effects, provided further distinguishing criteria. Of the 14 ads assessed, 4 ads (CP, Ba, AH, and DH) scored higher than the others. None of the four highest-scoring ads included the traditional Brief Summary. Among the four highest-scoring ads, no single front- or back-page layout stood out as being consistently better than the others, and it seems that the combi-

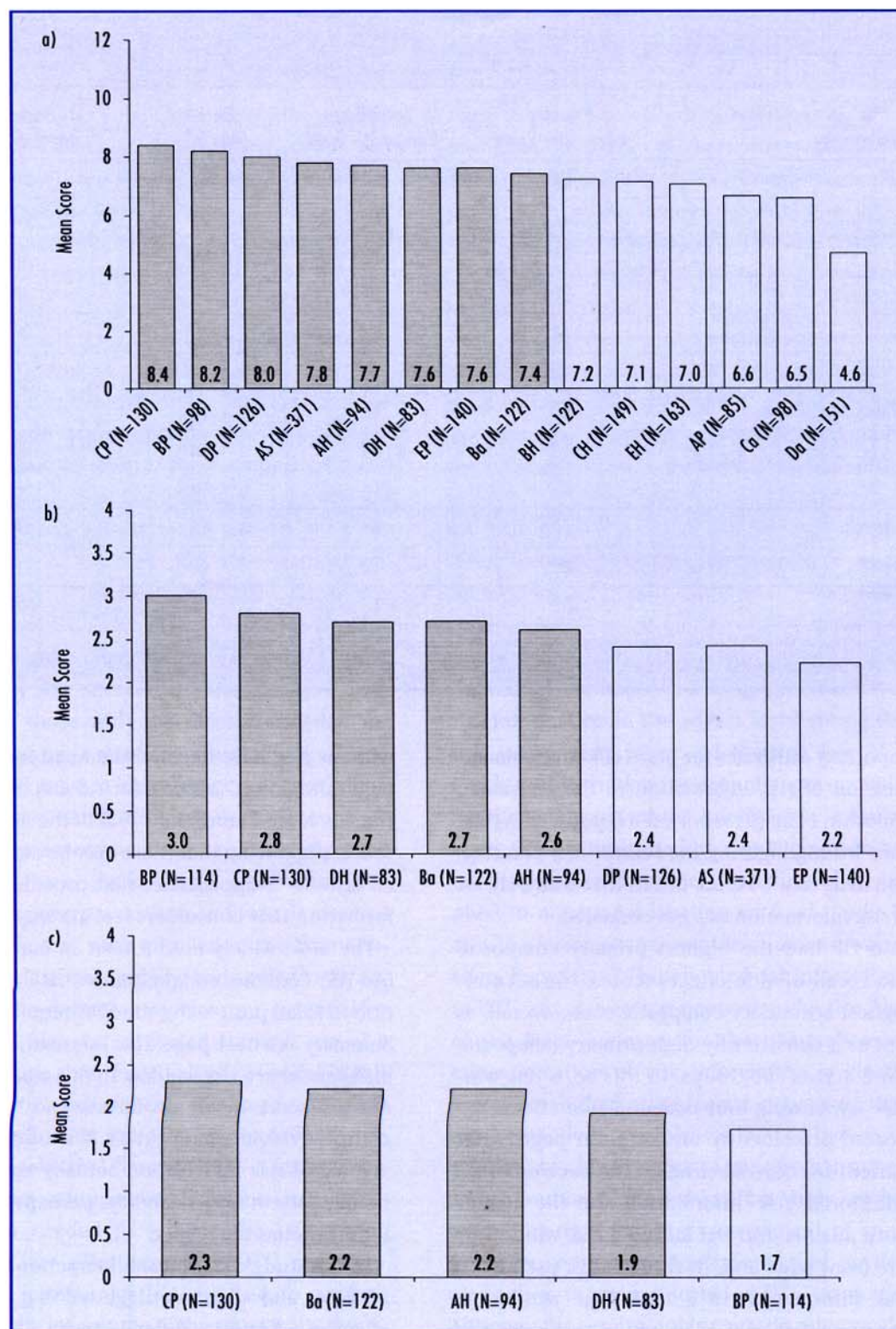


FIGURE 3

Scoring of ad prototypes. (a) Mean primary composite scores for all ad prototypes. Unshaded bars are for ads that had statistically significantly lower mean scores than the highest-scoring ad (CP). (b) Mean secondary composite scores for remaining eight ads. Unshaded bars are for ads that had statistically significantly lower mean scores than the highest-scoring ad (BP). (c) Mean number of side effects recalled through close-ended questioning. Only Ad BP scored significantly lower than the highest scoring ad (CP). All significant differences are at $P < .05$, using Tukey's multiple comparison procedure.

nation of a specific front and back page was key to an ad scoring highly. Front page E (ie, no risk information on front page) was not, however, represented in the highest-scoring ads.

According to the results of this study, including some risk information on the front page and highlighting risks in a framed window on either the front or back page, but not both, seem to be

TABLE 3

The Three Highest-Scoring Ad Layouts Population Subgroup in Depression Sufferers, Caregivers, General Population, and Overall					
Subgroup:		Primary Composite Score	Secondary Composite Score	Recall of Side Effects	Sum of Individual scores*
Depression sufferers	1.	<i>DH</i>	CH	<i>Ba</i>	<i>DH</i>
	2.	<i>CP</i>	<i>DH</i>	BH	<i>CP</i>
	3.	DP	BP	EH	<i>Ba</i>
Caregivers	1.	DP	BP	EH	<i>AH</i>
	2.	<i>CP</i>	CH	BH	DP
	3.	<i>AH</i>	<i>Ba</i>	<i>Ca</i>	<i>CP</i>
General population	1.	BP	BP	<i>CP</i>	<i>CP</i>
	2.	<i>CP</i>	BH	BH	BP
	3.	AS	<i>Ca</i>	<i>Ca</i>	BH
Overall	1.	<i>CP</i>	BP	BH	<i>CP</i>
	2.	BP	<i>Ba</i>	<i>CP</i>	BP
	3.	DP	<i>CP</i>	<i>Ca</i>	<i>AH</i>

Those ads scoring highest than all other ads in the primary analysis using the decision tree (ie, Ads CP, Ba, AH, and DH) are in italic.

*Sum of primary and secondary composite scores and recall of side effects score.

important attributes for more effective communication of risk information to the consumer. Woloshin et al. (9) reported a consumer preference for highlighting the *benefits* of a prescription drug in a DTC ad, but in that study, layout of risk information was not evaluated.

Ad CP had the highest primary composite and recall of side effects scores, the second-highest secondary composite score overall, as well as a consistently high primary composite score across subgroups. In this ad, a risk window containing four common side effects appeared prominently on the front page, while patient-friendly labeling on the back provided additional risk information for the reader. Both ads AH and DH lacked a risk window on the front page and, in these cases, presenting risk information in a back-page window as consumer-friendly, highlighted text appeared necessary for the ad to be one of the highest scoring. In the case of Ad Ba, a risk window displaying four common side effects, as well as contraindications and warnings, was clearly visible on the front page. Including this comprehensive risk information in a front-page

window may have negated the need for a back page altogether (absent for Ad Ba). None of the ads scored more than 75% of the maximum score, suggesting that there may be alternative ad layouts or approaches that provide the information that consumers feel are important.

The most widely used format in current use (Ad AS) contains comprehensive risk information in small print using the FDA-required Brief Summary as a back page. This information is not highlighted in a risk window. In this study, Ad AS did not score highly on format and layout or clarity of risk communication. Including such a volume of risk information actually appears to hinder patient understanding, perhaps because it overwhelms the reader.

In this study, a significant interaction between ad layout and subgroup suggested that the most effective ad layouts differ between depression sufferers, caregivers, and the general population. In a post hoc analysis, those four ad prototypes identified in the prespecified analysis for all respondents (ie, Ads CP, Ba, AH, and DH) all scored highly in at least one subgroup, with Ad CP scoring highly in all three subgroups. These

findings may assist with defining ad layouts that effectively communicate risk information to specific populations.

The FDA requires a fair balance of efficacy and safety information in the main body of the ad, but there is currently no regulatory standard or statutory criteria for determining how many side effects should be included. In this study, as the number of listed side effects increased, fewer readers accurately recalled any side effects correctly. Interestingly, no matter how many side effects were listed on the front page (4, 8, or 12), readers correctly recalled only one side effect on average, with no specific side effect consistently recalled. On the basis of these results, there appears to be no benefit in listing 8 or 12 side effects over 4 side effects. In this study population, side effects of medicine that cause patients to stop taking the medication, to drop out of the trial, or that last as long as the medicine is taken appeared most important to the readers, while temporary side effects and those occurring naturally in those with the disease/disorder appeared less important (data not shown). These data could assist in identifying criteria for which side effects should be selectively disclosed.

There are several limitations to this study, some of which have already been mentioned. This study considered only those individuals who had Internet access, were enrolled in the Harris Interactive database, and who had agreed to participate in this online survey. However, potential for selection bias was mitigated through use of a study design that treated all ads as equal in this regard, and adjustment was made through weighting so that the sample populations mirrored the relevant US populations in terms of demographics, attitudes, and behaviors. Further research is needed to validate the criteria for assessing the effectiveness of DTC advertisements in communicating risk and to confirm whether the magnitude of the statistically significant differences observed in this study truly translate to improved consumer understanding. For the assessment of side effect recall, only common, rather than serious, side effects were considered. However, The Henry J. Kaiser Family Foundation (10) reported that the public does

not have a strong sense of whether the potential side effects of medicines are serious or not. Moreover, in this study, ads always included the most serious side effects as warnings or contraindications. Ad layouts were only evaluated for one product, with a complex risk profile, and for one disease, but the sample population was stratified to include individuals with various levels of interest in the product. This study was focused on a specific treatment for major depressive disorder, and further study is needed to determine whether these results can be projected to other drug classes and disease states. This study was not designed to determine which common adverse events should be included in a print ad.

CONCLUSIONS

A number of print DTC ad layouts, with common themes, scored highly in this analysis, suggesting that there are several approaches to improving communication of safety information over traditional methods. Reducing the volume of risk information in the ad but highlighting the risk information presented through use of a highly visible window format enhances communication of important risk information. A similar approach has been used by regulators in an attempt to reduce consumer confusion when applied to nutritional labeling on food products and, to a lesser extent, over-the-counter medications. Repetition of highlighted risk information in DTC ads, however, is counterproductive. Use of the Brief Summary for the comprehensive communication of risk information is clearly less effective than other means, suggesting that regulators adopt new rules for DTC ad layouts as soon as possible in order to improve consumer understanding of drug risks. This study used a unique method for direct assessment of consumer perceptions on how information, particularly risks, is communicated in DTC print ads. Although the results of this study do not provide us with a definitive ad layout that is most effective in communicating risk information to the consumer, they provide a base from which future research may build and suggest ways to communicate risk more effectively than what the law currently requires.

Acknowledgments—We gratefully acknowledge Harris Interactive, Rochester, New York, for their assistance in study design and data collection; Foote, Cone & Belding, New York, for creating the ad prototypes; Timothy Franson, MD, FACP, William W. Chin, MD, and David Cox, PhD, Eli Lilly and Company, for critical review of this manuscript; the following individuals from the US Food and Drug Administration for assistance with the study protocol and interpretation of results—Robert Temple, MD, and Rachel Behrman, MD, Office of Medical Policy; Thomas Abrams, Kathryn Aikin, Amie Braman, and Professor Jack Swasy, Division of Drug Marketing, Advertising and Communication; Scott Gottlieb, MD, Deputy Commissioner for Medical and Scientific Affairs, and Nancy Ostrove, Senior Risk Communication Advisor, Office of the Commissioner.

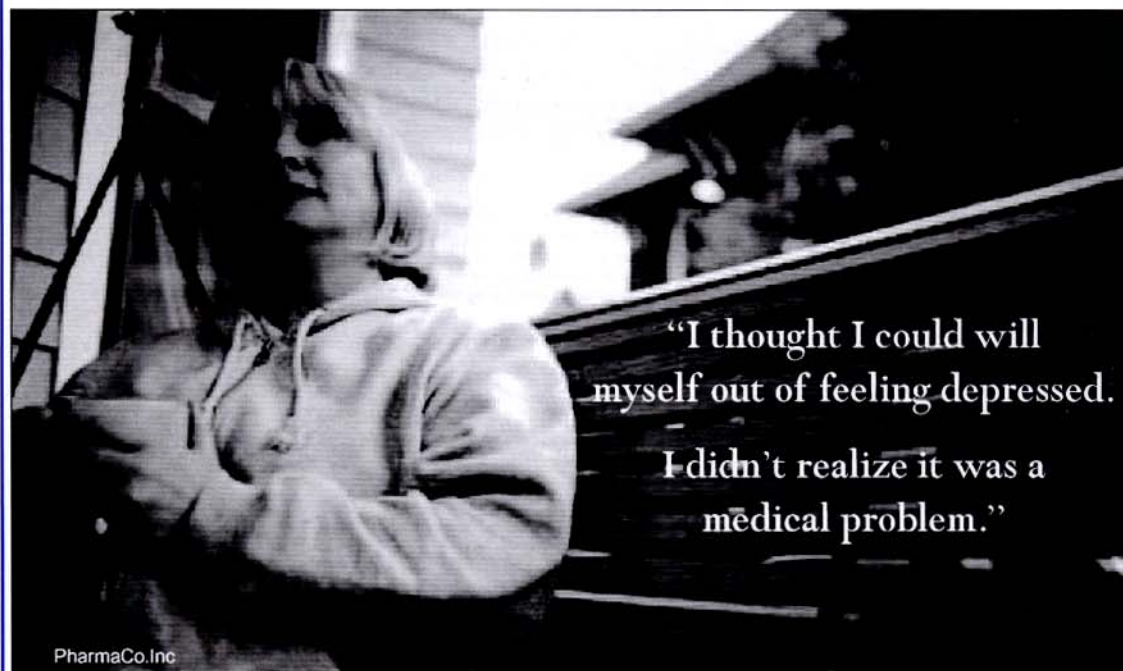
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Peter J. Pitts reports that the Center for Medicine in the Public Interest receives some unrestricted funding from pharmaceutical companies. David R. McAvoy has disclosed that he is an employee and company attorney for Eli Lilly and Co. Jennifer L. Stotka, Matthew D. Rotelli, Sherie A. Dowsett, Mary W. Elsner, and Stacy M. Holdsworth have disclosed that they are employees of Eli Lilly and Co.

Front Page C

FIGURE 4(A)



"I thought I could will myself out of feeling depressed. I didn't realize it was a medical problem."

Over 20 million Americans are affected by depression.
It can be treated. **Atentin** can help.

Have you been feeling unusually sad? Or irritable? Are you losing sleep? Even your interest in life? Do you have trouble concentrating? If you have symptoms like these every day and they last for more than two weeks you could be clinically depressed. It's a real illness. Depression can appear suddenly for no apparent reason. Or it can be triggered by stressful events in life. What can happen is that the level of serotonin (a chemical in your body) can drop. Atentin has been proven effective in the treatment of depression as it can help bring serotonin levels to normal.

Talk to your doctor or healthcare professional to see if Atentin is right for you.

Call 1-800-ATENTIN for more information
or visit www.atentin.com

What you need to know about Atentin

- **Side effects observed** during treatment that were determined to be most likely caused by Atentin were upset stomach, drowsiness, decreased appetite, and shakes, but these are usually mild and tend to go away.

This is not a complete list of all side effects that have been observed during Atentin use. Tell your doctor about any medical conditions you have and all medicines you are taking including dietary supplements. See your doctor because only your doctor can determine if Atentin or alternative treatments are right for you.

ATENTIN
moxetidine hydrochloride

Please see important patient information on the following page.

Layout of the four highest-scoring ads that were not statistically significantly different from each other based on results of the primary analyses

Fig. 4(a) CP; Fig. 4(b) AH; Fig. 4(c) DH; and Fig. 4(d) Ba.

FIGURE 4(A) cont.

Back Page P

Information for the patient

ATENTIN

marioxetine hydrochloride

Read this information completely before using Atentin.

(A-tentin). This is a summary about Atentin and does not contain complete information about your medicine. This information is not meant to take the place of discussions between you and your doctor. Talk with your doctor, pharmacist, or other healthcare professional if there is something you do not understand or if you want to learn more about Atentin. Always follow your doctor's instructions on how to take Atentin.

What is Atentin?

Atentin is a prescription medicine used to treat major depressive disorder, also known as depression.

What are the symptoms of Depression?

Symptoms of depression may include a combination of any of the following: always feeling sad or overwhelmed, feeling stressed or fatigued, loss of interest in things that you used to enjoy, trouble concentrating or making decisions, vague aches and pains that have gone unexplained, headaches, problems with digestion, changes in weight or appetite, or changes in sleep patterns (too much or too little). If symptoms have gone on for over two weeks and you feel that your interactions with others at work or at home are suffering, you should share this information with your doctor.

How does Atentin work?

Many doctors believe the symptoms of depression may be related to an imbalance in a natural chemical in the body called serotonin. Atentin works to restore the balance of serotonin. The actions of Atentin on serotonin may explain its effects in improving the symptoms of this condition.

Who should NOT take Atentin?

Do not take Atentin if you are:

- Taking a medicine known as a monoamine oxidase inhibitor (MAOI) or have stopped taking a MAOI within the last 2 weeks. Examples of MAOI medicines are Nardil® (phenylzine sulfate) and Parnate® (tranylcypromine sulfate). Taking Atentin with a MAOI may cause serious side effects that can be life threatening. Also you should not take a MAOI for at least 5 weeks after you stop taking Atentin.

- Taking Mellaril® (thioridazine). Taking Atentin with Mellaril® (thioridazine) can increase your chances of having a serious and potentially life-threatening heart problem. Also, you should not take Mellaril® (thioridazine) for at least 5 weeks after you stop taking Atentin.

- Allergic to Atentin or any of its ingredients.

What should I tell my doctor when taking Atentin?

- If you get a rash or hives while taking Atentin, call your doctor right away because this can be a sign of a serious medical condition.
- Tell your doctor if you are taking or plan to take prescription or non-prescription medicines, vitamins, dietary supplements, herbal remedies, or alcohol. Atentin can interact with some other medicines.
- Tell your doctor if you are taking Atentin and are taking or plan to take nonsteroidal anti-inflammatory drugs or aspirin since combined use of these drug products has been associated with an increased risk of bleeding.

Tell your doctor about all medical conditions you have, including if you...

- are pregnant, plan to become pregnant, or are breast feeding.
- have diabetes.
- have liver disease.
- have a history of seizures or mania.

How should I take Atentin?

- Take Atentin exactly as instructed by your doctor. Your doctor will usually start you on a low dose of Atentin. Your dose may be adjusted depending on your body's response to Atentin. Your dose will also depend on certain medical problems you have.
- If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only your regularly scheduled dose. Do not take more than the daily amount of Atentin that has been prescribed for you.
- Atentin can be taken with or without food.
- To help you remember to take Atentin, it may be best to take it at about the same time each day.
- Tell your doctor if your depression does not get better while taking Atentin. Your doctor may adjust your dose or give you a different medicine.
- Talk with your doctor about how long you should keep taking Atentin.
- Do not stop taking Atentin or change your dose, even if you feel better, without talking with your doctor.

What are possible side effects of Atentin?

- Side effects observed during treatment that were determined to be most likely caused by Atentin were upset stomach, drowsiness, decreased appetite, and shakes.
- Do not drive or operate other dangerous machinery until you know how Atentin affects you. Atentin can impair your judgment, thinking, and motor skills.
- Contact your doctor if you get a rash or hives while taking Atentin.

Tell your doctor about any side effects that bother you or won't go away. Your doctor may be able to help you manage the side effects.

These are not all the side effects of Atentin. For more information ask your doctor or pharmacist.

How do I store Atentin?

- Store Atentin at room temperature, 59° to 86°F (15° to 30° C).
- Keep the container tightly closed and protect from moisture.
- Keep Atentin and all medicines away from children.

General Information

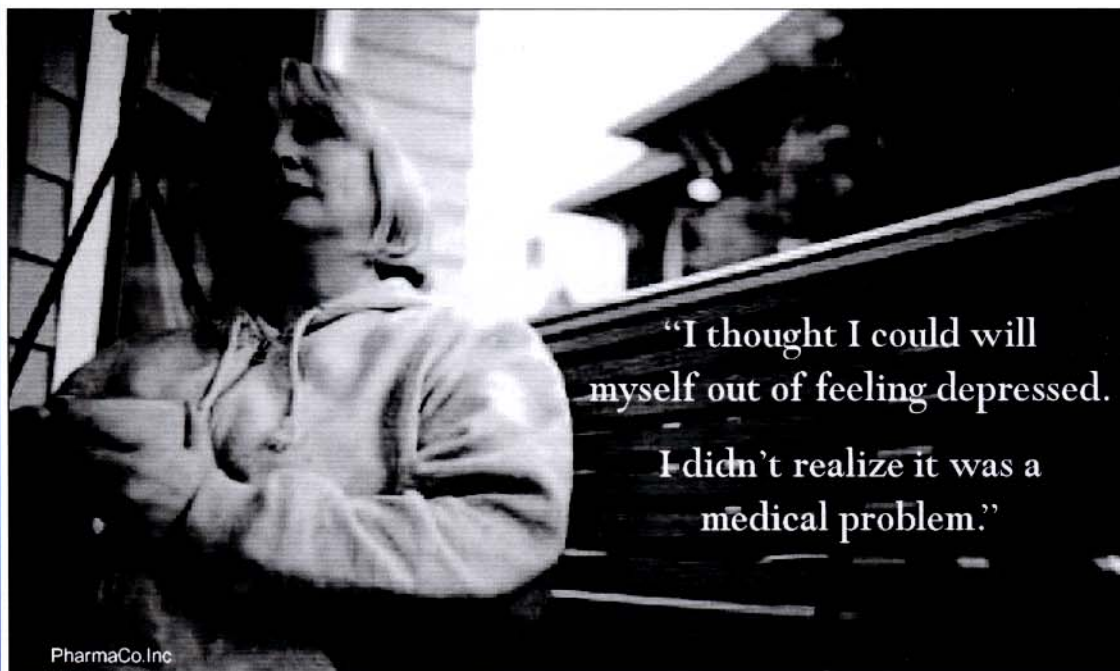
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Atentin for a condition for which it was not prescribed. Do not give Atentin to other people, even if they have the same symptoms that you have. It may harm them.

This summarizes important information about Atentin. If you would like more information, contact your doctor, pharmacist or other healthcare professional. You can also call 1-800-Pharmaco (1-800-123-4567).

Manufactured by:
Pharmaceutical Company

Front Page A

FIGURE 4(B)



"I thought I could will myself out of feeling depressed.

I didn't realize it was a medical problem."

Over 20 million Americans are affected by depression.
It can be treated. **Atentin** can help.

Have you been feeling unusually sad? Or irritable? Are you losing sleep? Even your interest in life? Do you have trouble concentrating? If you have symptoms like these every day and they last for more than two weeks you could be clinically depressed. It's a real illness.

Depression can appear suddenly for no apparent reason. Or it can be triggered by stressful events in life. What can happen is that the level of serotonin (a chemical in your body) can drop. Atentin has been proven effective in the treatment of depression as it can help bring serotonin levels to normal.

If you develop a rash or hives while taking Atentin, call your doctor right away because this can be a sign of a serious medical condition. You should not take Atentin at the same time as or within two weeks of stopping a MAO inhibitor (MAOI). Don't take a MAOI for at least 5 weeks after stopping Atentin. Also, you should not

take thioridazine at the same time as or within 5 weeks of stopping Atentin. Side effects observed during treatment that were determined to be most likely caused by Atentin were upset stomach, drowsiness, decreased appetite, and shakes, but these are usually mild and tend to go away.

This is not a complete list of all side effects that have been observed during Atentin use. Tell your doctor about any medical conditions you have and all medicines you are taking including dietary supplements. See your doctor because only your doctor can determine if Atentin or alternative treatments are right for you.

Talk to your doctor or healthcare professional to see if Atentin is right for you.

Call 1-800-ATENTIN for more information or visit www.atentin.com

ATENTIN
marioxetine hydrochloride

Please see important patient information on the following page.

FIGURE 4(B) cont.

Back Page H

Atentin

marioxetine hydrochloride

Atentin (A-tentin) is a prescription medicine used to treat the symptoms of major depressive disorder (also known as depression). Atentin contains marioxetine hydrochloride, a selective serotonin reuptake inhibitor.

You Should NOT Take Atentin if...

- you have taken MAO inhibitors such as Nardil® (phenylzine sulfate) or Parnate® (tranylcypromine sulfate) within the last two weeks.
- you are taking Mellaril® (thioridazine).
- you are allergic to Atentin or any of its components.

Be sure to tell your doctor about all medicines you are taking and all medical conditions you have, including if you...

- are taking or plan to take any prescription or nonprescription medicines, vitamins, dietary supplements, herbal remedies, or alcohol.
- have a history of seizures or mania.
- have liver problems.
- have diabetes.
- are pregnant, plan to become pregnant, or are breast feeding.

Side Effects

- Side effects observed during treatment that were determined to be most likely caused by Atentin were upset stomach, drowsiness, decreased appetite, and shakes.
- Tell your doctor immediately if you develop a rash while taking Atentin.
- Do not drive a car or operate dangerous machinery until you know what effect Atentin may have on you.

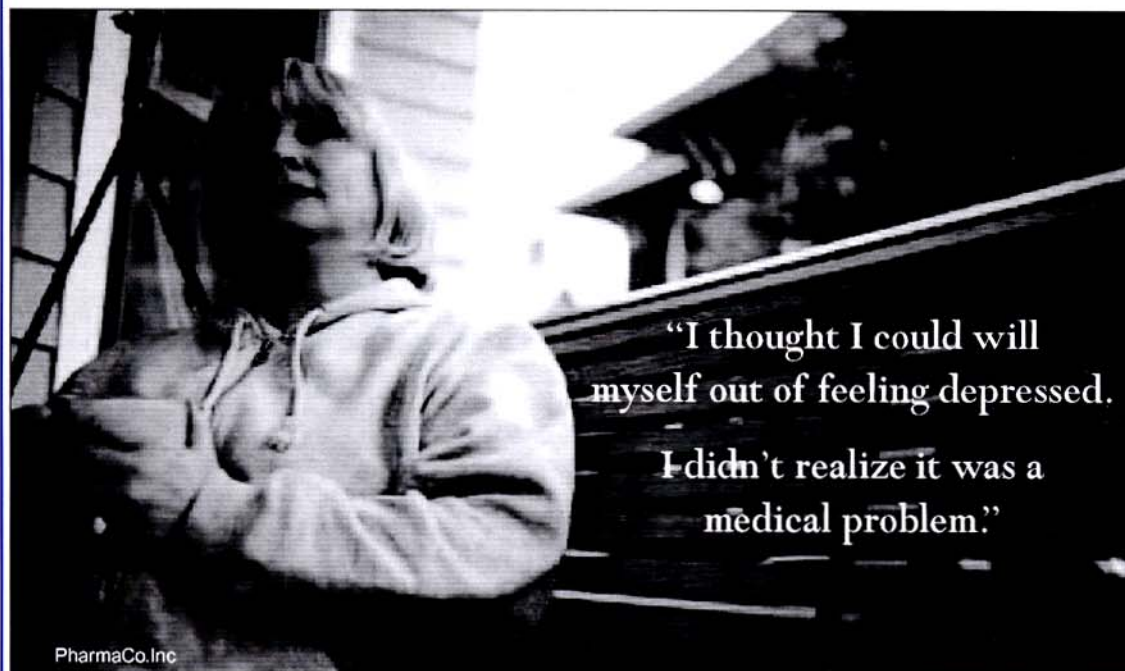
This listing of side effects is not complete. Your doctor, pharmacist, or other healthcare professional can discuss with you a more complete list of side effects that may occur when taking Atentin.

For additional information about Atentin, call 1-800-PharmaCo (1-800-123-4567).

Revised: March 2004
Pharmaceutical Company
Printed in USA

Front Page D

FIGURE 4(C)



Over 20 million Americans are affected by depression.
It can be treated. **Atentin** can help.

Have you been feeling unusually sad? Or irritable? Are you losing sleep? Even your interest in life? Do you have trouble concentrating? If you have symptoms like these every day and they last for more than two weeks you could be clinically depressed. It's a real illness. Depression can appear suddenly for no apparent reason. Or it can be triggered by stressful events in life. What can happen is that the level of serotonin (a chemical in your body) can drop. Atentin has been proven effective in the treatment of depression as it can help bring serotonin levels to normal.

Talk to your doctor or healthcare professional to see if
Atentin is right for you.

Call 1-800-ATENTIN for more information
or visit www.atentin.com

Always Consult Your Physician.

All prescription medications can cause some side effects, and some can be severe. Tell your doctor about any medical conditions you have and all medicines you are taking including dietary supplements. See your doctor, because only your doctor can determine if Atentin or alternative treatments are right for you.

ATENTIN
mefloquine hydrochloride

Please see important patient information on the following page.

FIGURE 4(C) cont.

Back Page H**ATENTIN**

marioxetine hydrochloride

Atentin (A-tentin) is a prescription medicine used to treat the symptoms of major depressive disorder (also known as depression). Atentin contains marioxetine hydrochloride, a selective serotonin reuptake inhibitor.

You Should NOT Take Atentin if...

- you have taken MAO inhibitors such as Nardil® (phenylzine sulfate) or Parnate® (tranylcypromine sulfate) within the last two weeks.
- you are taking Mellaril® (thioridazine).
- you are allergic to Atentin or any of its components.

Be sure to tell your doctor about all medicines you are taking and all medical conditions you have, including if you...

- are taking or plan to take any prescription or nonprescription medicines, vitamins, dietary supplements, herbal remedies, or alcohol.
- have a history of seizures or mania.
- have liver problems.
- have diabetes.
- are pregnant, plan to become pregnant, or are breast feeding.

Side Effects

- Side effects observed during treatment that were determined to be most likely caused by Atentin were upset stomach, drowsiness, decreased appetite, and shakes.
- Tell your doctor immediately if you develop a rash while taking Atentin.
- Do not drive a car or operate dangerous machinery until you know what effect Atentin may have on you.

This listing of side effects is not complete. Your doctor, pharmacist, or other healthcare professional can discuss with you a more complete list of side effects that may occur when taking Atentin.

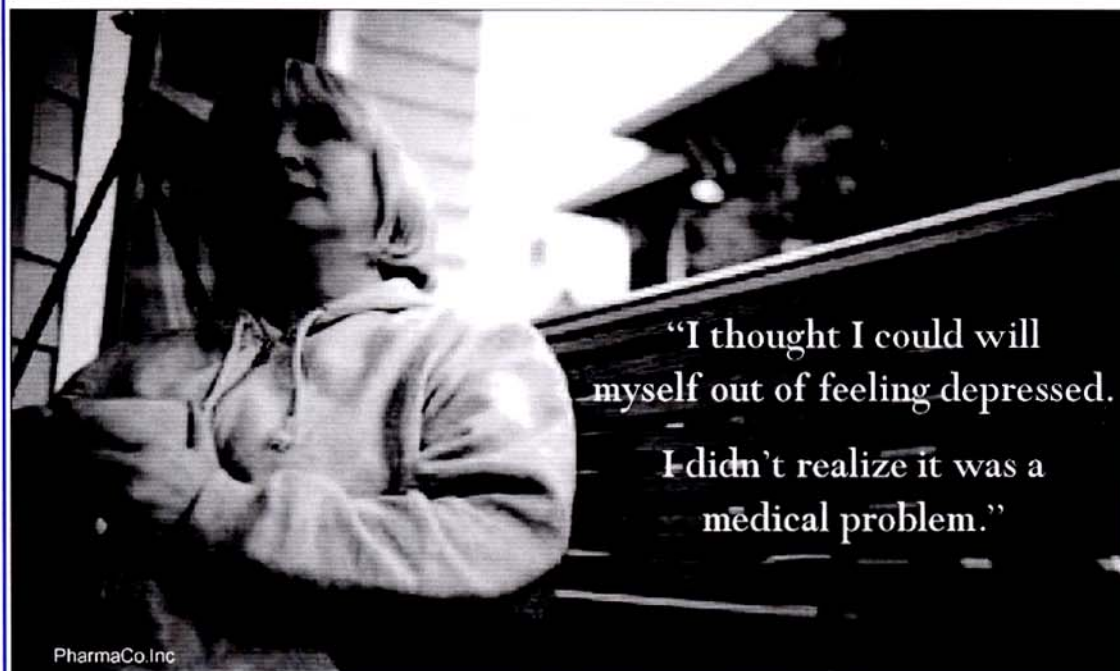
For additional information about Atentin, call 1-800-PharmaCo (1-800-123-4567).

Revised: March 2004
Pharmaceutical Company
Printed in USA

Front Page B

FIGURE 4(D)

(no back page)



"I thought I could will myself out of feeling depressed. I didn't realize it was a medical problem."

PharmaCo, Inc.

Over 20 million Americans are affected by depression.
It can be treated. **Atentin** can help.

Have you been feeling unusually sad? Or irritable? Are you losing sleep? Even your interest in life? Do you have trouble concentrating? If you have symptoms like these every day and they last for more than two weeks you could be clinically depressed. It's a real illness. Depression can appear suddenly for no apparent reason. Or it can be triggered by stressful events in life. What can happen is that the level of serotonin (a chemical in your body) can drop. Atentin has been proven effective in the treatment of depression as it can help bring serotonin levels to normal.

Talk to your doctor or healthcare professional to see if Atentin is right for you.

Call 1-800-ATENTIN for more information
or visit www.atentin.com

What you need to know about Atentin

- **You should not take Atentin if:**
 - you have taken MAO inhibitors such as Nardil® (phenylzine sulfate) or Parnate® (tranylcypromine sulfate) within the last two weeks.
 - you are taking Mellaril® (thioridazine).
 - you are allergic to Atentin or its ingredients.
- **Tell your doctor immediately** if you develop a rash while taking Atentin.
- **Side effects observed** during treatment that were determined to be most likely caused by Atentin were upset stomach, drowsiness, decreased appetite, and shakes, but these are usually mild and tend to go away.

This is not a complete list of all side effects that have been observed during Atentin use. Tell your doctor about any medical conditions you have and all medicines you are taking including dietary supplements. See your doctor because only your doctor can determine if Atentin or alternative treatments are right for you.

ATENTIN
marloxetine hydrochloride