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Author: Jennifer R. Havens Carl G. Leukefeld Angela M.

DeVeaugh-Geiss Paul Coplan Howard D. Chilcoat

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The impact of a reformulation of extended-release oxycodone designed to deter abuse

in a sample of prescription opioid abusers\*

**Authors:** Jennifer R. Havensa, Carl G. Leukefelda, Angela M. DeVeaugh-Geissb, Paul Coplanb, Howard D. Chilcoatb

**Affiliations:**

a Department of Behavioral Science, University of Kentucky College of Medicine, 333 Waller Avenue, Suite 480, Lexington, KY, USA 40504 b Risk Management and Epidemiology, Purdue Pharma L.P., One Stamford Forum, Stamford, CT, USA 06901

**Corresponding author:**

Jennifer R. Havens Associate Professor Center on Drug and Alcohol Research Department of Behavioral Science University of Kentucky College of Medicine 333 Waller Avenue, Suite 480 Lexington, KY 40504 859-323-6553 jennifer.havens@uky.edu

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**ABSTRACT**

**Background:** Prescription opioid abuse is a significant public health concern that requires strategies to reduce its impact, including development of abuse deterrent formulations. OxyContin®, an extended-release oxycodone (ERO) formulation, has been widely abused. This study assessed the effects of reformulated ERO, designed to be more difficult to manipulate for purposes of intranasal and intravenous abuse, on patterns of opioid abuse among a sample of individuals from rural Appalachia with a history of ERO abuse. **Methods:** Structured interviews assessing opioid abuse (past 30-day abuse and retrospectively reported abuse prior to the reformulation in August 2010) were completed by 189 individuals between December 2010 and September 2011. **Results:** The past 30-day prevalence and frequency of reformulated ERO abuse through any route (33%, 1.9 days/month), snorting (5%, 0.2 days/month), and injecting (0.5%, <0.1 days/month) were low and infrequent compared to that of IR oxycodone (any route: 96%, 19.5 days/month; snorting: 70%, 10.3 days/month; injecting: 51%, 10.5 days/month) and retrospectively reported abuse of original ERO in August 2010 (any route: 74%, 13.4 days/month; snorting: 39%, 6.0 days/month; injecting: 41%, 8.6 days/month). After the reformulation, the prevalence of original ERO abuse significantly declined while abuse of reformulated ERO remained steadily low. Heroin abuse was rare in this sample. **Conclusions:** In this sample, abuse of reformulated ERO was low, and lower than abuse of original ERO retrospectively and IR oxycodone concurrently, particularly through injecting and snorting routes of administration. There was no evidence to suggest that reformulated ERO became a substitute for original ERO. **KEYWORDS:** Tamper resistant formulation, abuse deterrent formulation, extended-

release oxycodone, ER oxycodone, prescription opioid abuse

**1. INTRODUCTION**

While there is a demonstrated therapeutic benefit of prescription opioids to pain patients, abuse continues to be a significant public health concern in the United States (US; Compton and Volkow, 2006; Zacny et al., 2003) and an emerging problem globally (Degenhardt et al., 2006; Fountain et al., 2000; Tang et al., 2005; Kumar and Agrawal, 2012). The persistence of prescription opioid abuse has spurred the development of strategies to reduce its impact (Office of National Drug Control Policy, 2012a). One strategy is the development of formulations that are more difficult to manipulate for purposes of abuse. Some opioids have recently been reformulated (Embeda package insert, 2009; Opana package insert, 2011; OxyContin package insert, 2013), and there is laboratory-based and clinical pharmacological evidence (Cone et al., 2013; Sellers et al., 2013; Perrino et al., 2013) as well as emerging evidence in national surveillance systems (Butler et al., 2013; Severtson et al., 2013; Cicero et al., 2012) on their impact. However, existing surveillance systems utilize cross-sectional averages and do not provide detailed measures of abuse or within-individual changes in abuse patterns. Therefore, additional research is warranted that examines patterns of abuse of reformulated opioids, particularly in populations that were abusing original formulations of these drugs.

Although many individuals abuse opioids orally and most new opioid users initiate through oral routes (Katz et al., 2011), there is often progression to non-oral routes (Hays, 2004; Katz et al., 2011), and a longer duration of abuse is associated with snorting or injecting (Butler et al., 2010; Hays, 2004). Additionally, opioid abuse, is particularly prevalent in many rural areas of the US (Havens et al., 2007a, 2007b; Young and Havens, 2012; Leukefeld et al., 2002; Cicero et al., 2007): three studies found high rates of injection drug use (frequently OxyContin® [oxycodone HCl controlled release tablets], an extended-release oxycodone [ERO] formulation manufactured by Purdue Pharma L.P.) among prescription opioid users in rural cohorts (Havens et al., 2007a, 2007b; Young and Havens, 2012), including those where there was little use before the prescription drug epidemic (Leukefeld et al., 2002). Furthermore, Young and Havens (2012) reported that almost half of injection drug users reported initiating injecting with ERO. Recent data also suggest high rates of hepatitis C among rural prescription opioid users, which is largely attributed to injection drug use, particularly prescription opioids (Havens et al., 2013). Crushing and snorting prescription opioids have also been reported among rural drug users (Young et al., 2010). Given the adverse medical outcomes associated with non-oral abuse, it is important to understand the impact of abuse deterrent formulations on abuse, particularly in areas with high rates of opioid abuse through non-oral routes of administration.

In April, 2010, the Food and Drug Administration (FDA) approved a reformulation of ERO (OxyContin®, manufactured by Purdue Pharma L.P.), that is bioequivalent to the original formulation when taken as directed, but has physicochemical properties designed to make it more difficult to manipulate for abuse. In August 2010, manufacturer shipments of original ERO ceased and shipments of reformulated ERO began. By December 2010 and December 2011, 90% and 99%, respectively, of the ERO dispensed in the US was reformulated ERO, with a similar distribution in Kentucky (82% and 99% in the same time periods, respectively; IMS Health NPA), although there was evidence of continued availability of original ERO for abuse despite limited

availability through legitimate channels (Butler et al., 2013). Therefore, the primary

objective of this study was to describe the extent to which reformulated ERO was abused relative to other opioids, particularly other oxycodone products such as original ERO and immediate-release (IR) oxycodone, in a sample of individuals in rural Kentucky with an established history of ERO abuse. Other opioids, including IR oxycodone, were included to differentiate temporal or secular trends from ERO-specific changes, as well as to explore patterns of possible substitution from one opioid to another. Additionally, we compared abuse of ERO and IR oxycodone to retrospective reports of use prior to the reformulation (August, 2010).

This study complements an epidemiologic study program using several large national surveillance systems to evaluate the effects of the introduction of reformulated ERO on patterns of opioid abuse (Butler et al., 2013; Severtson et al., 2013) by assessing effects among a cohort of individuals with an established history of ERO abuse prior to the ERO reformulation in rural Appalachia, one of the regions of the country most impacted by prescription opioid abuse.

**2. METHODS**

Individuals who abused ERO before the reformulation in August 2010 were recruited from rural Perry County, Kentucky, using a purposive sampling technique. Flyers were posted in the study office and areas around Perry County that have been utilized for prior studies (Havens et al., 2008) to recruit initial seed participants, who were in turn asked to recruit up to 3 peers. Individuals were eligible if they were at least 18 years of age and had abused ERO in the 6 months preceding the introduction of reformulated ERO in August, 2010. Consenting participants were interviewed privately

at the study office by a single trained interviewer. Participants were compensated $50

for their time and up to $30 (total) for recruitment of additional participants. The Institutional Review Board from the University of Kentucky approved the study protocol.

An interviewer-administered questionnaire was used to assess history of substance use/abuse in addition to demographics, employment, medical history, and psychiatric history. The questionnaire was a modified version of Addiction Severity Index (McLellan, 1992), including additional drugs and information about routes of administration. Use of prescription opioids, alcohol, and illegal drugs were assessed.

To measure substance abuse, participants were asked about abuse (defined as use of substances to get high), including routes of administration, during: 1) lifetime; 2) the 30 days prior to the release of the reformulation (August, 2010); and 3) in the 30 days prior to interview in the post-reformulation period (conducted December, 2010 through September, 2011). To anchor questions about drug abuse in August, 2010, participants were asked about their abuse before the Black Gold festival, a well-known event in the area that coincided with the initial shipments of reformulated ERO. Anchoring is a common technique used to improve the accuracy of recall (Barsky, 2002).

The Mini Neuropsychiatric Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; Sheehan et al., 1998) was used to measure psychiatric diagnoses common in substance-using and chronic pain populations at the time of the interview (i.e., current major depressive disorder or generalized anxiety disorder, and lifetime history of opioid dependence).

The prevalence of abuse was based on the number of participants reporting ≥1

day of abuse (any route, snorting, injecting, oral – swallowing). The frequency of abuse (days/month) was calculated as the mean days of abuse overall and via each route; participants who did not report abuse were included as 0 days/month. While the primary focus of this report is non-oral routes of administration, abuse via any route provides an overall measure of abuse encompassing both oral and non-oral routes; the prevalence and frequency of oral abuse are also shown in the Figures to provide an overall picture of the abuse of reformulated ERO within this community.

In order to evaluate changes in abuse over time, past 30-day abuse is described both for the entire sample (n=189) and divided into 4 mutually exclusive sub-groups based on date of interview (period 1 [T1]: December, 2010 through February, 2011, n=51; period 2 [T2]: March through April, 2011, n=64; period 3 [T3]: May through June, 2011, n=43; period 4 [T4]: July through September, 2011, n=31). While these subgroups were not defined a priori, they were selected to provide approximately equal time windows over the course of the post-reformulation interview period.

Regression models with Generalized Estimated Equations (GEE), which account for assessment of correlated outcomes within the same respondent, were used to explore abuse (both changes in the same drug across time periods or across drugs within a time period) (Liang and Zeger, 1986; Zeger and Liang, 1986). Poisson regression models with GEE were used for prevalence of abuse data. Negative binomial regression models (estimating rate ratios) with GEE were used for models with drug abuse frequency as the outcome. All models were run separately for each route of administration (any route, snorting, injecting). The models included indicator variables

for drug (original ERO, reformulated ERO, any ERO, IR oxycodone) and time, as well

as the time*x*drug interaction terms. IR oxycodone was the referent when comparing across drugs within a time period; time period 1 (T1) was the referent when comparing within drugs across time periods. Pre- vs. post-reformulation comparisons were also based on Poisson models with GEE (prevalence) or negative binomial models with GEE (frequency) and were run separately for ERO and IR oxycodone, both overall, and stratified by interview period. Post-reformulation trends were tested using the Cochran-Armitage test for trend (prevalence) and the regression model including categorized date of interview as a continuous variable (frequency).

All analyses were conducted in SAS version 9.2.

**3. RESULTS**

*3.1 Demographics and drug abuse history*

Overall, 365 individuals were screened and 194 were eligible (171 had no ERO abuse in the 6 months prior to the reformulation in August 2010). Of these, 192 were interviewed, and 189 were included in the analysis (3 participants were excluded: one with no substance abuse history, one with no lifetime abuse of ERO, and one who was discontinued from the study after threatening the study staff).

Of the 189 participants, 54.5% were male and nearly all were white (97.9%) (Table 1). All participants reported ever abusing IR oxycodone formulations, 51.3% reported ever abusing reformulated ERO, and nearly all (>90%) reported lifetime abuse of hydrocodone, methadone, benzodiazepines, cocaine, alcohol, and marijuana. Most had a history of injection drug abuse (81.5%), and among those, nearly all (96.1%) had injected prescription opioids. Almost all participants had a history of opioid dependence

(96.3%). The demographic characteristics of the sample were similar regardless of

recruitment date.

Based on retrospective reports, in the month prior to the introduction of reformulated ERO most participants reported abuse of original ERO (74%) and IR oxycodone (74%) (Table 1). Other opioid products abused by a large portion of the subjects were hydrocodone (63%) and methadone (48%), with slightly lower prevalence for buprenorphine (22%) and oxymorphone (12%). Heroin abuse was uncommon (5%). The scope of the current analysis is oxycodone abuse; results for other opioids are presented in supplemental tables only.

*3.2 Prevalence of abuse*

The prevalence of reformulated ERO abuse in the 30 days preceding the interview via any route of administration, which includes both oral and non-oral routes of administration, was relatively low (prevalence=33%; Figure 1). Analysis of trends by date of interview showed no significant differences in prevalence among those interviewed more proximally vs. distally in time from the introduction of the reformulation (Figure 1; test for trend, p=0.19).1 In contrast, the overall prevalence of IR oxycodone abuse, which was not available in an abuse deterrent formulation, was high (prevalence=96%) and remained high regardless of interview date (Figure 1; test for trend, p=0.46). As shown in Table 2, the relative prevalence of abuse of reformulated ERO was significantly lower than that for IR oxycodone in each of the four post-reformulation interview periods, as well as overall across all time periods (RR=0.34, 95%CI 0.28-0.42). Additionally, the past 30-day prevalence of reformulated ERO abuse

1 Results of the trend analysis, which describe within opioid changes over the post‐reformulation period, are provided in detail in Supplemental Table 1 and can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:... .

was significantly lower than retrospectively-reported abuse of original ERO in August,

2010 (Table 3; 33% vs. 74%; RR=0.45, 95%CI 0.35-0.56).

The prevalence of abuse of reformulated ERO via snorting and injecting were low (5% [n=10] and 0.5% [n=1], respectively) and showed no increasing trend over time (Figure 1; test for trend: p=0.32 and p=0.21, respectively). These findings are in contrast to the relatively high prevalence of IR oxycodone abuse via snorting (70%) and injecting (51%). Notably, the prevalence of IR oxycodone abuse by snorting and injecting remained high throughout the study (Figure 1; test for trend: p=0.34 and p=0.86, respectively), while that for original ERO declined. The relative prevalence of reformulated ERO abuse via these routes was significantly lower than that for IR oxycodone in each of the four post-reformulation interview periods as well as across all interview periods (Table 2; snorting: RR=0.08, 95%CI 0.04-0.14; injecting: RR=0.01, 95%CI 0.002-0.07). The prevalence of reformulated ERO abuse was also significantly lower than retrospectively reported abuse of original ERO in August 2010 for both snorting (5% vs. 39%, respectively [RR=0.14, 95%CI 0.07-0.26] and injecting (0.5% vs. 30%, respectively [RR=0.01, 95%CI 0.002-0.09]) (Table 3).

As shown in Figure 1, in the first two interview periods the prevalence of original ERO abuse (any route, snorting, and injecting) was similar to retrospective reports of abuse in August, 2010; however, the prevalence of abuse declined significantly after the first two interview periods (test for trend: any route, p<0.0001; snorting, p<0.0001; injecting, p<0.001). As the prevalence of original ERO abuse declined, a significant difference vs. the prevalence of abuse of IR oxycodone emerged, and this difference increased in magnitude over time (RR=0.86 in T1 vs. 0.17 in T4; Table 2). Due to the

high prevalence of original ERO abuse relative to reformulated ERO abuse, trends for

prevalence of any ERO (original or reformulated) abuse were similar to those for original ERO (Figure 1, Table 2).

*3.3 Frequence of abuse (mean days per month)*

Frequency of abuse provides further understanding of abuse patterns and paralleled the trends in prevalence. Among all participants (n=189), abuse of reformulated ERO was infrequent regardless of interview date (mean days/month: any route=1.9, snorting=0.2, injecting=0.02; Figure 2, Table 3). Only 1 participant reported injecting with a frequency of 1 day/month. Among those who reported snorting (n=10), the frequency of abuse was 4.2 days/month. As shown in Figure 2, there was no significant increase in frequency of reformulated ERO abuse via any route, snorting, or injecting during the study period (test for trend: p=0.15, p=0.28, and p=0.96, respectively). The frequency of reformulated ERO abuse was also significantly lower than concurrently reported IR oxycodone abuse (Table 2) and retrospectively reported abuse of original ERO in August, 2010 (Table 3). While the frequency of reformulated ERO abuse remained low with a relatively flat trend over the study period (tests for trend p > 0.05), the frequency of IR oxycodone abuse remained high and relatively steady with an average frequency of abuse of approximately 20 days/month for any route of administration and approximately 10 days/month for both snorting and injecting (Figure 2; tests for trend: any route, p=0.31; snorting, p=0.38; injecting, p=0.93).

As shown in Figure 2, the frequency of original ERO abuse via any route, snorting, and injecting declined during the study. The decline in frequency was observed earlier in the post-reformulation interview period, in contrast to the prevalence of abuse, which remained relatively high through the first half of the post-reformulation period (Figure 1). However, the greatest declines in frequency of original ERO were observed in the more distal interviews, consistent with declining availability of original ERO (Figure 2) with declining trends for any route (p<0.0001), snorting (p=0.08), and injecting (p=0.02)). Additionally, the frequency of original ERO abuse was consistently and significantly lower than that of IR oxycodone, though the magnitude of the difference was greatest among those interviewed more distally from the introduction of the reformulation (Table 2). The trend for any ERO (original or reformulated) paralleled the trends in original ERO due to the relatively high frequency of abuse of original vs. reformulated ERO (Figure 2 and Table 2).



*3.4 IR Oxycodone and heroin abuse*

Both the prevalence and frequency of IR oxycodone abuse were significantly higher than retrospectively reported abuse in August, 2010 (prevalence: 96% vs. 74%, respectively [RR=1.30, 95%CI 1.19-1.42]; frequency: 19.5 vs. 12.8 days/month [RR=1.53, 95%CI 1.34-1.74]; Table 3]. Similarly, the prevalence and frequency of IR oxycodone abuse were significantly higher as compared to estimates in August, 2010 for both snorting and injecting (Table 3). There was no observed increase in heroin abuse, with only 1 participant reporting abuse of heroin in the 30 days prior to the post-reformulation interview) (results not shown), as compared to 10 individuals [5%] retrospectively in August, 2010. 2

**4. DISCUSSION**

2 Additional details on the frequency of abuse for other (non‐oxycodone) opioids among the entire sample (n=189) are provided in Supplemental Table 2 and can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:... .

In this cohort, which was selected for a history of original ERO abuse, the prevalence and frequency of reformulated ERO abuse through any route, snorting, and injecting routes of administration were low and infrequent compared to both concurrently-reported IR oxycodone abuse and retrospectively-reported original ERO abuse. In contrast to the ubiquitous abuse of IR oxycodone in the 30 days prior to assessment (prevalence=96%, frequency=19.5 days/month), with high frequency through non-oral routes such as snorting and injecting, only 33% reported abuse of reformulated ERO in the month before the interview (overall frequency=1.9 days/month) despite availability through retail pharmacies for the duration of the study (IMS NPA Health). While original ERO was abused by more than half of those interviewed within seven months after the introduction of reformulated ERO, the prevalence and frequency of abuse declined among those interviewed later, consistent with a declining number of original ERO prescriptions dispensed in pharmacies nationally. In contrast, the trend for both reformulated ERO and IR oxycodone abuse remained relatively flat regardless of interview date. Abuse of reformulated ERO was substantially lower than that of IR oxycodone overall and via injecting and snorting. The low prevalence and frequency of abuse of reformulated ERO relative to that of original ERO and IR oxycodone, especially via routes that require tampering, support the abuse-deterrent qualities of reformulated ERO.

When shipments of original ERO by the manufacturer ceased in August, 2010, abuse continued despite reduced availability through legal channels, although both the prevalence and frequency decreased over time. Despite replacing almost all of the ERO dispensed from pharmacies by December 2010 nationally (≥90%) and in Kentucky

(82%; IMS NPA Health), reformulated ERO abuse was infrequent and remained

relatively constant throughout the interview period. Because reformulated ERO was available through legal channels, there may have been a reduction in supply though channels involving diversion due to less demand, as indicated by a decline in diversion events for ERO reported by the RADARS system (Severtson et al., 2013). Overall, findings indicate that reformulated ERO did not become a substitute for original ERO, particularly for preferred routes of administration (i.e., snorting and injecting).

Findings in this report are consistent with those of other studies that have reported lower rates of reformulated ERO abuse, particularly through non-oral routes of administration that require tampering. In a large sample of individuals (n=140,496) assessed for substance abuse treatment in the US, the overall rate of reformulated ERO abuse via any route and non-oral routes decreased by 41% for any route and 66% for non-oral routes compared to historical rates of original ERO in the period prior to launch of the reformulation (Butler et al., 2013). In another independent study of individuals with opioid dependence entering substance abuse treatment before or after the ERO reformulation (n=2,566), Cicero et al. (2012) observed a decline in the proportion of respondents selecting ERO as the primary drug of abuse after the reformulation. Our study extends findings from these studies by exploring changes within individuals with a recent history of ERO abuse in an area of the country with epidemic opioid abuse. Further, this study examines quantitative measures of patterns of abuse that were not considered by other studies, including frequency of abuse through specific routes of administration.

Despite reductions in ERO abuse after the reformulation, there was no apparent

impact on overall opioid abuse in this sample due to the high levels of IR oxycodone abuse, which was not available in an abuse-deterrent formulation during the study period. These results are not unexpected because though ERO was reformulated with physicochemical barriers to breaking, crushing or dissolving intended to deter abuse, the reformulation does not treat the underlying abuse and addiction that is driving those behaviors. Furthermore, there is some evidence that individuals in this sample may have moved to another available formulation of their preferred substance, IR oxycodone (i.e., a balloon effect), though pre-reformulation abuse was assessed retrospectively. Qualitative interviews conducted in a subset of the sample (n=25) also provide compelling support for the observed shift from original ERO to IR oxycodone formulations (Buer et al., in press). Therefore, although replacing original with reformulated ERO appeared to have an impact on ERO abuse, in order to have an impact on overall prescription opioid abuse, it may be necessary for all opioid formulations to have abuse-deterrent features.

Cicero et al. (2012) also describe a balloon effect in a population of people in substance abuse treatment with diagnosed prescription opioid dependence; though abuse of ERO as the primary drug of abuse declined substantially, the prevalence of heroin abuse nearly doubled. It should be noted that Cicero et al. did not examine whether frequency of abuse of other prescription opioids increased even though prevalence of these opioids was relatively stable after the reformulation, whether the increase in prevalence of heroin abuse reflected frequent versus occasional abuse, or whether there was an impact of the reformulation on the onset of new opioid users as

opposed to the prevalence of opioid abuse among well-established users. In contrast to

these findings, in this sample from rural Kentucky, heroin abuse was uncommon even after reformulated ERO was introduced. Rather, individuals appeared to prefer IR oxycodone, a preference which also been observed in other studies of this population (see Havens et al., 2007b; Young et al., 2012; Young and Havens, 2012). Thus, while both our study and Cicero et al. (2012) suggest the concept of a “balloon effect,” the pattern of changes in preference may vary depending on the characteristics of the study population, including factors such as accessibility of other prescription opioids or heroin.

 Though findings from this study indicate that the reformulation reduced ERO abuse via non-oral routes that require tampering, the findings need to be interpreted in light of the study limitations. The population was from rural Kentucky, an area of the US with epidemic prescription opioid problems; therefore, results may not be generalizable to all individuals who abuse opioids. However, as described by the FDA in the draft guidance for Evaluation and Labeling of Abuse Deterrent Opioids (FDA Guidance for Industry, 2013), studies in select populations of individuals who abuse opioids provide important supplemental data which contributes to the totality of evidence related to abuse deterrence.

 A further limitation is that there was no differentiation between single-entity and combination IR oxycodone, which are likely to have different patterns of abuse; however, the high frequency of non-oral abuse is consistent with abuse of single-entity oxycodone. Additionally, the study was not initiated until December, 2010, following the FDA Advisory Committee meeting on the post-marketing studies for reformulated OxyContin and Embeda in October, 2010 (FDA Advisory Committee Transcript, 2010).

Consequently, reports of abuse of original ERO and other drugs prior to the

reformulation in August, 2010 were assessed retrospectively, 4 to 13 months after the introduction of the reformulation. While anchoring to a well-known festival in the area was used to improve recall, reports of abuse in these more distal interviews could be influenced, in part, by recall bias. Therefore, although there was some evidence of a balloon effect, alternative explanations cannot be ruled out.

 An offsetting strength is the use of past 30-day, self-reported drug abuse. Self-reported drug use has been examined extensively, and studies have consistently reported that self-reported drug use is a valid measure of actual drug use (Darke, 1998; Kokkevi et al., 1997), with shorter time frames exhibiting less bias than more lengthy recall periods (Gfroerer et al., 2004). Therefore respondents are likely to report about drug use behavior in the 30 days prior to the interview (post-reformulation) with relatively high accuracy and there is no indication of differential reporting of reformulated ERO compared to other opioids. Furthermore, despite decreasing original ERO abuse and steadily high levels of IR oxycodone abuse, there was no apparent increase in reformulated ERO abuse throughout the recruitment period, despite a large number of prescriptions being filled at retail pharmacies nationwide (over 90,000 prescriptions per week nationally beginning in late October, 2010; IMS Health NPA).

 While these results support the abuse-deterrent qualities of reformulated ERO, it is critical that abuse-deterrent formulations be viewed in the appropriate context. Abuse deterrent formulations can play a role as part of a comprehensive approach to addressing the prescription drug abuse epidemic, such as that developed by the Office of National Drug Control Policy, which includes efforts aimed at education, monitoring,

proper disposal, and enforcement (Office of National Drug Control Policy, 2012b). The

introduction of a single abuse-deterrent formulation cannot prevent adverse changes in the patterns of abuse of other non-abuse deterrent products, and as a result, cannot mitigate the adverse medical and public health consequences of prescription opioid abuse entirely. However, as demonstrated by this study, among this sample of individuals with a history of original ERO abuse, the low rates of reformulated ERO abuse, particularly by injecting and snorting, indicate that abuse-deterrent formulations can be an important and effective part of this overall strategy to address the prescription drug abuse epidemic.

**FIGURE LEGENDS**

**Figure 1.** Prevalence of abuse of original ER oxycodone (ERO), reformulated ERO, any ERO, and IR oxycodone based on current recall (December 2010 through September 2011) and retrospective recall (August 2010)

Pre‐reformulation (August 2010): n=189

Post‐reformulation December 2010 – February 2011: n=51; March ‐April 2011: n=64; May – June 2011: n=43; July – September 2011, n=31 Error bars are 95% Confidence Intervals (CI). Dotted horizontal lines represent the mean values

for each drug. Note: Error bars are not visible for reformulated ERO injecting in all post‐reformulation periods. **Figure 2.** Frequency of abuse of original ER oxycodone (ERO), reformulated ERO, any ERO, and

IR oxycodone based on current recall (December 2010 through September 2011) and retrospective recall (August 2010)

Pre‐reformulation (August 2010): n=189 Post‐reformulation December 2010 – February 2011: n=51; March ‐April 2011: n=64; May – June 2011: n=43; July – September 2011, n=31

Error bars are 95% Confidence Intervals (CI). Dotted horizontal lines represent the mean values for each drug. Note: participants who reported no abuse were included in analysis as 0 days/month. Note: Error bars are not visible for reformulated ERO injecting/snorting in all post‐

reformulation periods.

**REFERENCES**

Barsky, A.J., 2002. Forgetting, fabricating, and telescoping: the instability of the medical history. Arch. Intern. Med. 162, 981-984.

Buer, L-M., Havens, J.R., Leukefeld, C.G., Changing drug use patterns in rural Appalachia: a qualitative analysis. Subst. Use Misuse: In press.

Butler, S.F., Black, R.A., Serrano, J.M., Wood, M.E., Budman, S.H., 2010. Characteristics of prescription opioid abusers in treatment: prescription opioid use history, age, use patterns, and functional severity. J. Opioid Manage. 6, 239-41, 246-52.

Butler, S.F., Cassidy, T.A., Chilcoat, H., Black, R.A., Landau, C., Budman, S.H., Coplan, P.M., 2013. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. J. Pain 14, 351-358.

Cicero, T.J., Ellis, M.S., Surratt, H.L., 2012. Effect of abuse-deterrent formulation of OxyContin. N. Engl. J. Med. 367, 187-189.

Cicero, T.J., Surratt, H., Inciardi, J.A., Munoz, A., 2007. Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States. Pharmacoepidemiol. Drug Safe. 16, 827-840.

Compton, W.M., Volkow, N.D., 2006. Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug Alcohol Depend. 81, 103-107.

Cone, E.J., Giordano J., Weingarten B., 2013. An iterative model for in vitro laboratory

assessment of tamper deterrent formulations. Drug Alcohol Depend.131,100-105.

Darke, S., 1998. Self-report among injecting drug users: a review. Drug Alcohol Depend. 51, 253-63; discussion 267-8.

Degenhardt, L., Day, C., Dietze, P., Pointer, S., Conroy, E., Collins, L., Hall, W., 2005. Effects of a sustained heroin shortage in three Australian States. Addiction 100, 908-920.

Embeda [package insert], 2012. King Pharmaceuticals Inc., Bristol, TN.

FDA Advisory Committee Transcript (October 21), 2010. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting Announcement. Thursday, October 21, 2010. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm193298.htm. Accessed July 2, 2013.

FDA Guidance for Industry, 2013. Abuse Deterrent Opioids – Evaluation and Labeling Draft Guidance. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory. Accessed July 2, 2013.

Fountain, J., Strang, J., Gossop, M., Farrell, M., Griffiths, P., 2000. Diversion of prescribed drugs by drug users in treatment: analysis of the UK market and new data from London. Addiction 95, 393-406.

Gfroerer, J., Hughes, A., Chromy, J., Heller, D., Packer, L., 2004. Estimating trends in substance use based on reports of prior use in a cross-sectional survey. In: Cohen, S.B., Lepkowski, J.M. (Eds.), Eighth Conference on Health Survey Research Methods: Conference proceedings [Peachtree City, GA] (HHS Publication No. PHS 04-1013, pp. 29-34). U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, MD. [Available as a PDF at http://www.cdc.gov/nchs/data/misc/proceedings\_hsrm2004.pdf]

Havens, J.R., Lofwall, M.R., Frost, S.D., Oser, C.B., Leukefeld, C.G., Crosby, R.A., 2013. Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. Am. J. Public Health 103, e44-52.

Havens, J.R., Walker, R., Leukefeld, C.G., 2008. Prescription opioid use in the rural Appalachia: a community-based study. J. Opioid Manage. 4, 63-71.

Havens, J.R., Walker, R., Leukefeld, C.G., 2007a. Prevalence of opioid analgesic injection among rural nonmedical opioid analgesic users. Drug Alcohol Depend. 87, 98-102.

Havens, J.R., Oser, C.B., Leukefeld, C.G., Webster, J.M., Martin, S.S., O'Connell, D.J., Surratt, H.L., Inciardi, J.A., 2007b. Differences in prevalence of prescription opiate misuse among rural and urban probationers. Am. J. Drug Alcohol Abuse 33, 309­

317.

Hays, L.R., 2004. A profile of OxyContin addiction. J. Addict. Dis. 23, 1-9.

Katz, N., Dart, R.C., Bailey, E., Trudeau, J., Osgood, E., Paillard, F., 2011. Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. Am. J. Drug Alcohol Abuse 37, 205.

Kokkevi, A., Richardson, C., Palermou, B., Leventakou, V., 1997. Reliability of drug dependents' self-reports. Drug Alcohol Depend. 45, 55-61.

Kumar, M.S., Agrawal, A., 2012. Scale-up of opioid substitution therapy in India: opportunities and challenges. Int. J. Drug Policy 23, 169-170.

Leukefeld, C.G., Logan, T.K., Farabee, D., Clayton, R., 2002. Drug use and AIDS: estimating injection prevalence in a rural state. Subst. Use Misuse 37, 767-782.

Liang, K.-Y. and Zeger, S. L., 1986. Longitudinal data analysis using generalized linear models. Biometrika 73, 13-22.

McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., Argeriou, M., 1992. The fifth edition of the Addiction Severity Index. J. Subst. Abuse Treat. 9, 199-213.

Office of National Drug Control Policy, 2012a. 2012 National Drug Control Strategy. http://www.whitehouse.gov/ondcp/2012-national-drug-control-strategy. Accessed October 18, 2012.

Office of National Drug Control Policy, 2012b. Prescription Drug Abuse. http://www.whitehouse.gov/ondcp/prescription-drug-abuse. Accessed October 18, 2012.

Opana [package insert], 2011. Lincoln, NE: Novartis Consumer Health, Lincoln,

NEOxyContin [package insert], 2013. Purdue Pharma L.P., Stamford, CT.

Perrino, P.J., Colucci, S.V., Apseloff, G., Harris, S.C., 2013. Pharmacokinetics, tolerability, and safety of intranasal administration of reformulated OxyContin® tablets compared with original OxyContin® tablets in healthy adults. Clin. Drug Investig. 33, 441-449.

Sellers, E.M., Perrino, P.J., Colucci, S.V., Harris, S.C., 2013. Attractiveness of reformulated OxyContin(R) tablets: assessing comparative preferences and tampering potential. J. Psychopharmacol. [Epub ahead of print]

Severtson, S.G., Bartelson, B.B., Davis, J.M., Munoz, A., Schneider, M.F., Chilcoat, H., Coplan, P.M., Surratt, H., Dart, R.C., 2013. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release Oxycodone in 2010. J. Pain [Epub ahead of print].

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59, 22­

33.

Tang, Y.L., Zhao, D., Zhao, C., Cubells, J.F., 2006. Opiate addiction in China: current situation and treatments. Addiction 101, 657-665.

Young, A.M., Havens, J.R., 2012. Transition from first illicit drug use to first injection

drug use among rural Appalachian drug users: a cross-sectional comparison and

retrospective survival analysis. Addiction 107, 587-596.

Young, A.M., Havens, J.R., Leukefeld, C.G., 2012. A comparison of rural and urban nonmedical prescription opioid users' lifetime and recent drug use. Am. J. Drug Alcohol Abuse 38, 220-227.

Young, A.M., Havens, J.R., Leukefeld, C.G., 2010. Route of administration for illicit prescription opioids: a comparison of rural and urban drug users. Harm Reduct. J. 7, 24-7517-7-24.

Zacny, J., Bigelow, G., Compton, P., Foley, K., Iguchi, M., Sannerud, C., 2003. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. Drug Alcohol Depend. 69, 215-232.

Zeger, S. L., Liang, K.-Y., 1986. Longitudinal data analysis for discrete and continuous outcomes. Biometries 42, 121-130.

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**Contributors**

Jennifer R. Havens, Carl Leukefeld, Howard Chilcoat, and Paul Coplan designed the study and wrote the protocol. Jennifer R. Havens and Carl Leukefeld oversaw the data collection. Jennifer R. Havens and Angela DeVeaugh-Geiss conducted the statistical analyses. Angela DeVeaugh-Geiss and Jennifer R. Havens wrote the first draft of the manuscript. All authors assisted in providing substantive and editorial direction to all drafts of the manuscript. All authors contributed to and have approved the final manuscript.

**Conflict of Interest**

Carl G. Leukefeld is employed at the University of Kentucky and has received extramural funding from the National Institutes of Health, the State of Kentucky, and Purdue Pharma. Jennifer R. Havens is employed at the University of Kentucky and has received extramural funding from the National Institutes of Health and Purdue Pharma. Angela DeVeaugh-Geiss, Howard Chilcoat, and Paul Coplan are employees of Purdue Pharma L.P. Angela DeVeaugh-Geiss has previously been employed at GlaxoSmithKline and Merck & Co, Inc. Howard Chilcoat has been previously employed at GlaxoSmithKline.

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**Table 1. Demographic and drug abuse characteristics of individuals with an established history of original ER oxycodone abuse in Perry, Kentucky, in the United States (N=189).**

|  |  |  |
| --- | --- | --- |
|  | N  | **%**  |
| Total  | 189  | 100  |
| Gender, male  | 103  | 54.5  |
| Age, median (IQR)  | 32 (27, 39)  |
| White  | 185  | 97.9  |
| Years of education, median (IQR)  | 12 (10, 12)  |
| Full-time employment  | 45  | 23.8  |
| DSM-IV disorders  |  |  |
| Major depressive disorder  | 102  | 54.0  |
| Generalized anxiety disorder  | 87  | 46.0  |
| Opioid dependence  | 182  | 96.3  |
| Lifetime injection drug abuse  | 154  | 81.5  |
| Injected prescription opioids (n=154)  | 148  | 96.1  |
|  | Lifetime  | August 2010  |
| Abuse of Opioids  | N  | %  | N  | %  |
| Original ER oxycodone  | 189  | 100  | 139  | 73.5  |
| Reformulated ER oxycodone  | 97  | 51.3  | NA  | NA  |
| Hydrocodone  | 185  | 97.9  | 119  | 63.0  |
| Buprenorphine† |  142  | 75.1  | 42  | 22.2  |
| Methadone† |  176  | 93.1  | 90  | 47.6  |
| IR oxycodone  | 189  | 100  | 140  | 74.1  |
| Avinza‡ (morphine sulfate extended-release capsules)  | 8  | 4.2  | 0  | 0  |
| Opana‡ (oxymorphone hydrochloride tablets)  | 98  | 51.9  | 23  | 12.2  |
| Opana ER‡ (oxymorphone hydrochloride extended-release tablets)Accepted Manuscript | 9  | 4.8  | 1  | 0.5  |
| Embeda‡ (morphine sulfate and naltrexone hydrochloride)  | 1  | 0.5  | 0  | 0  |
| Heroin  | 59  | 31.2  | 10  | 5.3  |
| Abuse of other substances  |  |  |  |  |
| Benzodiazepines  | 177  | 93.7  | 105  | 55.6  |
| Cocaine  | 173  | 91.5  | 37  | 19.6  |

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Crack cocaine  | 103  | 54.5  | 11  | 5.8  |
| Methamphetamine  | 80  | 42.3  | 5  | 2.7  |
| Alcohol  | 187  | 98.9  | 83  | 43.9  |
| Marijuana  | 181  | 95.8  | 97  | 51.3  |

IQR, interquartile range; ER, extended release; IR, immediate release; NA, not applicable

† Illicit methadone and illicit buprenorphine were explicitly identified to differentiate illicit abuse from use by participants formally participating in substance abuse treatment programs.

‡ Because these products were newer to the market, participants were asked explicitly about the branded product unless otherwise noted.

**Table 2. Differences in prevalencea and frequencyb of abuse of ER oxycodone (original, reformulated, any) vs. IR oxycodone during pre-reformulation (pre-ORF) and post-reformulation (post-ORF) periods**

**Pre-ORF Post-ORF RR (95%CI) RR (95%CI) Overall Overall T1 T2 T3 (Aug 2010) (Dec 10-Sep 11) (Dec 10-Feb 11) (Mar 11- Apr 11) (May 11-Jun N=189 N=189 N=51 N=64 N= 43**

**Prevalence – Any Routec**

IR oxycodone Ref. Ref. Ref. Ref. Ref.

ER oxycodone Reformulated NA 0.34 (0.28, 0.42) 0.38 (0.26, 0.55) 0.34 (0.24, 0.50) 0.38 (0.26, 0.5 Original 0.99 (0.90, 1.09) 0.62 (0.55, 0.70) 0.86 (0.76, 0.98) 0.82 (0.71, 0.94) 0.36 (0.24, 0.5 Any NA 0.76 (0.70, 0.84) 0.98 (0.92, 1.05) 0.93 (0.84, 1.04) 0.57 (0.44, 0.7

**Prevalence – Snortingc**

IR oxycodone Ref. Ref. Ref. Ref. Ref.

ER oxycodone Reformulated NA 0.08 (0.04, 0.14) 0.06 (0.03, 0.35) 0.04 (0.01, 0.16) 0.13 (0.05, 0.3 Original 0.84 (0.72, 0.99) 0.56 (0.47, 0.67) 0.84 (0.65, 1.08) 0.73 (0.57, 0.93) 0.26 (0.14, 0.4 Any NA 0.61 (0.52, 0.73) 0.87 (0.69, 1.10) 0.75 (0.60, 0.94) 0.39 (0.23, 0.6

**Prevalence – Injectingc**

IR oxycodone Ref. Ref. Ref. Ref. Ref.

ER oxycodone Reformulated NA 0.01 (0.002, 0.07) 0.04 (0.01, 0.28) 0 0 Original 1.32 (1.09, 1.60) 0.59 (0.49, 0.71) 0.88 (0.71, 1.10) 0.76 (0.59, 0.98) 0.29 (0.16, 0.5 Any NA 0.59 (0.49, 0.71) 0.88 (0.71, 1.10) 0.76 (0.59, 0.98) 0.29 (0.16, 0.5

**Frequency – Any Routec**

IR oxycodone Ref. Ref. Ref. Ref. Ref.

ER oxycodone Reformulated NA 0.01 (0.07, 0.15) 0.11 (0.05, 0.24) 0.12 (0.06, 0.22) 0.09 (0.04, 0.1 Original 1.05 (0.90, 1.23) 0.35 (0.28, 0.43) 0.52 (0.39, 0.69) 0.45 (0.32, 0.59) 0.16 (0.08, 0.3 Any NA 0.43 (0.36, 0.52) 0.60 (0.46, 0.78) 0.54 (0.41, 0.70) 0.25 (0.14, 0.4

**Frequency – Snortingc**

IR oxycodone Ref. Ref. Ref. Ref. Ref.

ER oxycodone Reformulated NA 0.02 (0.01, 0.05) 0.02 (0.004, 0.11) 0.003 (0.001, 0.01) 0.03 (0.01, 0.1 Original 0.80 (0.64, 1.02) 0.33 (0.24, 0.44) 0.52 (0.32, 0.83) 0.44 (0.29, 0.66) 0.11 (0.04, 0.2 Any NA 0.35 (0.26, 0.46) 0.54 (0.34, 0.85) 0.44 (0.29, 0.66) 0.14 (0.06, 0.3

**Frequency – Injectingc**

IR oxycodone Ref. Ref. Ref. Ref. Ref.

ER oxycodone Reformulated NA 0.001 (0.0001, 0.004) -d -d -d Original 1.50 (1.19, 1.89) 0.34 (0.26, 0.46) 0.52 (0.35, 0.76) 0.43 (0.27, 0.67) 0.19 (0.08, 0.4 Any NA 0.34 (0.26, 0.46) 0.52 (0.35, 0.76) 0.43 (0.27, 0.67) 0.19 (0.0, 0.4

ER, extended release; IR, immediate release; NA, not applicable; Ref., referent; pre-ORF, pre-reformulation (August 2010); post-ORF, post-reformulation (December 2010 through September 2011); T1, Dec10-Feb11; T2, Mar11­Apr11; T3, May11-Jun11; T4, Jul11-Sep11 a Poisson regression models included the outcome (dichotomous drug abuse) as well as the following dependent variables: an indicator variable for drug (original ERO, reformulated ERO, any ERO, IR oxycodone), an indicator variable for recruitment time (T1, T2, T3, T4) and time by drug interaction terms. b Negative binomial regression models included the outcome (frequency [days/month] of abuse) as well as the following dependent variables: an indicator variable for drug (original ERO, reformulated ERO, any ERO, IR oxycodone), an indicator variable for recruitment time (T1, T2, T3, T4) and time by drug interaction terms. c Abuse via any route was based on a question regarding overall past 30 day abuse of each drug (any routes of administration including both oral and non-oral routes). Specific routes of administration questions were asked as a series of separate questions addressing 30-day abuse by each route. Note: participants who reported no abuse were

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included in calculation of mean days of abuse per month (abuse frequency) as 0 days/month. d Only 1 individual reported 1 day of abuse or reformulated ERO via injecting during the first recruitment period (T1).

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**Table 3. Prevalence (95% CI) and frequency (mean days of abuse per month [95% CI]) in August 2010 (pre-reformulation, pre-ORF) and in the past 30 days (post­reformulation, post-ORF) for original ER oxycodone, reformulated ER oxycodone, and IR oxycodone (n=189)**

**ER oxycodone IR oxycod Pre-ORF Post-ORF Pre (original) Pre-ORF Post-OR vs. Original Original**b **Reformulated Post (reformulated)a**

**(N=189) (N=189**

**(N=189) (n=189) (n=189) RR (95% CI)**

**Prevalence**

0.45

Any Routec 74% 60% 33% 74% 96%

(0.35, 0.56)

0.14

Snortingc 39% 39% 5% 47% 70%

(0.07, 0.26)

0.01

Injectingc 41% 30% 0.5% 31% 51%

(0.002, 0.09)

**Frequency**

13.4 6.8 1.9 0.14 12.8 19.5

Any Routec (11.7, 15.2) (5.3, 8.2) (1.2, 2.7) (0.10, 0.22) (11.1, 14.4) (17.9, 21

Snortingc 6.0 3.3 0.2 0.04 7.4 10.3 (4.6, 7.3) (2.3, 4.4) (0.02, 0.4) (0.01, 0.10) (5.9, 8.9) (8.7, 11.

Injectingc 8.6 3.6 <0.1 0.001 5.7 10.5 (6.8, 10.4) (2.4, 4.8) (0.00, 0.02) (0.0001, 0.004) (4.3, 7.2) (8.6, 12.

ER, extended release; IR, immediate release; pre-ORF, pre-reformulation (August 2010); post-ORF, post-reformulation (December 2010 through September 2011) a Pre vs. Post reflects pre-reformulation original ERO vs. post-reformulation reformulated ERO b Overall results for ERO should be interpreted with caution given the significant decline observed in prevalence of original ERO abuse over the recruitment period. No significant differences over the recruitment period were observed in the prevalence of reformulated ERO or IR oxycodone. c Overall abuse based on a question regarding overall past 30 day abuse of each drug (any routes of administration). Specific routes of administration questions were asked as a series of separate questions addressing 30-day abuse by each route. *Note:* participants who reported no abuse were included in calculation of mean days of abuse per month (abuse frequency) as 0 days/month.

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**Figure**

Any Route Oral -Swallowing Snorting Injecting



|  |  |  |  |
| --- | --- | --- | --- |
| Aug10 Dec10­Mar11­May11­Jul11­ | Aug10 Dec10­Mar11­May11­Jul11­ | Aug10 Dec10­Mar11­May11­Jul11­ | Aug10 Dec10­Mar11­May11­Jul11­ |
| n=189 Feb11 Apr11 Jun11 Sep11  | n=189 Feb11 Apr11 Jun11 Sep11  | n=189 Feb11 Apr11 Jun11 Sep11  | n=189 Feb11 Apr11 Jun11 Sep11  |
| n=51  | n=64  | n=43  | n=31  | n=51  | n=64  | n=43  | n=31  | n=51  | n=64  | n=43  | n=31  | n=51  | n=64  | n=43  | n=31  |

Any Route Oral -Swallowing Snorting Injecting



|  |  |  |  |
| --- | --- | --- | --- |
| Aug10 Dec10­Mar11­May11­Jul11­ | Aug10 Dec10­Mar11­May11­Jul11­ | Aug10 Dec10­Mar11­May11­Jul11­ | Aug10 Dec10­Mar11­May11­Jul11­ |
| n=189 Feb11 Apr11 Jun11 Sep11  | n=189 Feb11 Apr11 Jun11 Sep11  | n=189 Feb11 Apr11 Jun11 Sep11  | n=189 Feb11 Apr11 Jun11 Sep11  |
| n=51  | n=64  | n=43  | n=31  | n=51  | n=64  | n=43  | n=31  | n=51  | n=64  | n=43  | n=31  | n=51  | n=64  | n=43  | n=31  |