Extreme Work Requirement of EG-001, an Abuse-Deterrent, Extended-Release Morphine Product, as Demonstrated With the ALERRT℠ Visual Analog Scales

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Poster #30

Introduction

- The launch of the first abuse-deterrent (AD) opioid formulation in 2010 was followed by a reduction in prescription opioid overdoses.[1]
  - However, there was migration of substance abusers to non-AD prescription opioid formulations and to heroin.[1,2]
  - Greater availability of opioid formulations with AD technology is needed to reduce opioid abuse without decreasing access to the analgesic efficacy of opioids for legitimate pain patients.
- Generally, AD technology aims to prevent abuse of extended-release (ER) opioids
  - AD technologies based on physical/chemical barriers present obstacles to manipulation and/or maintain ER properties despite manipulation. Some of these products also have the additional advantage of preventing the risk of accidental misuse by pain patients (ie, chewing).
  - Alternative AD technology relies on manipulation to release a sequestered antagonist that blocks opioid effects but also has the risk of precipitating opioid withdrawal in legitimate pain patients who accidentally crush or chew their medication.[3]
- Laboratory-based studies designed to determine the relative difficulty of compromising AD properties of a formulation are a key component in the evaluation and labeling of AD opioids by the US Food and Drug Administration.[4]
- EG-001 (Egalet Corporation, Wayne, PA) is a novel AD, ER morphine product candidate incorporating a proprietary technology (Guardian™; Egalet), which is a polymer matrix tablet technology that utilizes a novel manufacturing process, plastic injection molding, which results in tablets with controlled release properties as well as physical and chemical barriers that have been demonstrated to resist both common and more rigorous methods of manipulation which limits particle size reduction.

Objective

- The goal of this study was to measure the amount of "work" (ie, combination of time, effort, and resources) required to physically compromise the AD technology of EG-001 tablets compared with marketed formulations of immediate-release (IR; generic; Roxane Laboratories, Columbus, OH) and ER morphine (MS Contin®; Purdue Pharma, LP, Stamford, CT) using standardized manipulation techniques and a newly developed instrument, the Assessing Labor, Effort and Resources Required for Tampering scales (ALERRT℠; **Pinney**Associates, Bethesda, MD), visual analog scales or VASs.

Methods

Study Design

- Four trained technicians from an independent laboratory (DrugScan, Horsham, PA) performed unblinded, standardized, physical manipulations of the 4 opioid formulations and assessed the amount of work (all tools) and time (3 preselected tools) that were applied using the VASs comprising ALERRT.

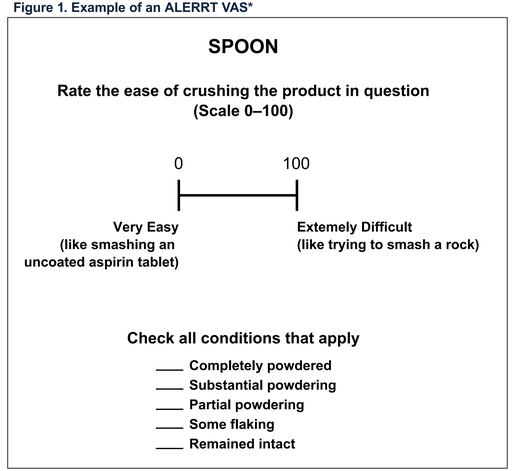
Opioid Formulations Tested

- EG-001 60-mg tablets
- EG-001 100-mg tablets
- IR morphine sulfate 30-mg tablets
- ER morphine 60-mg tablets

Assessments

- ALERRT consists of a series of 100-point VASs (0 = very easy to 100 = extremely difficult) specific to 10 household tools commonly used by recreational users of prescription drugs to manipulate opioid products **(Figure 1)**.

Figure 1. Example of an ALERRT VAS*



ALERRT VAS=Assessing Labor, Effort and Resources Required for Tampering visual analog scale.
*Representative VAS from 1 of the 10 household tools.

- The 10 household tools used in ALERRT were
  - Spoons (Venice®, 18/10 stainless steel teaspoons)
  - Mortar/pestle (CoorsTek®, porcelain ceramic mortar and pestle #60313)
  - Pill crusher (Apex®, pill pulverizer #70029)
  - Hammer (Tekton®, 16-oz wood claw hammer)
  - Food grater (Microplane®, 5100506, 18/8-gauge stainless steel blade)
  - Foot file (PedEgg®, pedicure foot file)
  - Razor blade (GEM®, stainless steel uncoated single-edge industrial blades, thickness 0.0009 in, Fisher Cat #62-0167)
  - Spice grinder (Waring® Commercial, model WSG30)
  - Coffee grinder (Cuisinart®, model DCG-12BC)
  - Coffee grinder (Krups®, 203 electric spice and coffee grinder)
- Descriptive terms such as, but not limited to, "completely powdered", "partial powdering", "some flaking", and "difficult to cut" were used to characterize the results of the manipulations.

Statistical Analysis

- A simple random permutation was used to assign tablet order to tool for each technician.
- The primary analysis was of the relative resistance of the 4 opioid formulations to manipulation by each of the household tools, quantified as a mean VAS score for each tool and presented with descriptive statistics (mean, SD; median, range).

Results

ALERRT VAS Scores

- VAS scores for EG-001 100-mg and 60-mg tablets were comparable and at the higher end of the scale, as were scores for ER morphine and IR morphine tablets, which were at the lower end of the scale **(Table 1)**.

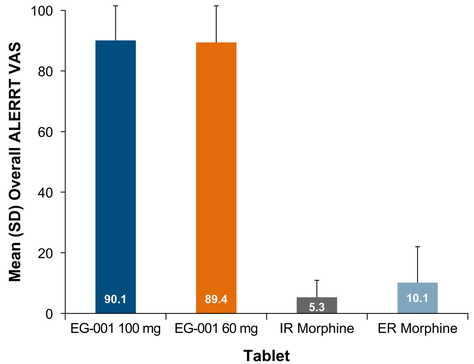
Table 1. Mean (SD) ALERRT VAS Scores for Each Tool Between Different Tablets

Tool	EG-001 100 mg (N=4)	EG-001 60 mg (N=4)	IR Morphine 30 mg (N=4)	ER Morphine 60 mg (N=4)
Spoon	99.5 (1.0)	98.5 (1.3)	7.5 (9.8)	10.3 (15.9)
Mortar/pestle	99.3 (1.0)	99.0 (0.8)	3.5 (3.1)	5.3 (6.1)
Pill crusher	98.5 (1.7)	98.8 (0.5)	2.8 (1.5)	15.8 (15.0)
Hammer	88.3 (14.2)	89.8 (11.1)	2.0 (0.8)	17.5 (22.6)
Food grater	86.8 (11.9)	90.8 (9.5)	4.8 (3.4)	2.3 (1.5)
Foot file	95.5 (3.0)	93.5 (3.5)	14.8 (6.6)	11.3 (7.1)
Razor blade	83.0 (12.1)	71 (9.8)	4.5 (3.9)	7.8 (8.9)
Spice grinder	77.0 (14.3)	81.0 (14.3)	4.3 (3.2)	6.0 (8.0)
Cuisinart® coffee grinder	92.3 (4.5)	96.5 (3.7)	6.3 (6.8)	12.8 (10.8)
Krups® coffee grinder	81.3 (13.2)	75.3 (11.0)	2.3 (1.9)	12.5 (15.3)

ALERRT VAS=Assessing Labor, Effort and Resources Required for Tampering visual analog scale; ER=extended release; IR=immediate release.

- Overall mean VAS scores indicated that EG-001 100-mg and 60-mg tablets were extremely difficult to manipulate **(Figure 2)**.
  - In contrast, mean VAS scores for ER and IR morphine tablets were consistently low, indicating that these tablets were easily manipulated.

Figure 2. Overall Mean ALERRT VAS Scores*



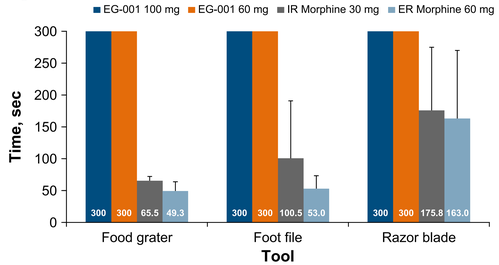
ALERRT VAS=Assessing Labor, Effort and Resources Required for Tampering visual analog scale; ER=extended release; IR=immediate release.
*Values are the mean (SD) of the ALERRT VAS scores across all 10 tools used for manipulation of the tablets.

- The hardness of EG-001 tablets resulted in mechanical failure or damage to some of the tools used for tablet crushing and grinding.
  - Damage included a broken pestle, cracked coffee grinder lids, and broken coffee grinders.
- For some tools, EG-001 100-mg and 60-mg tablets had VAS scores up to 10-fold higher compared with ER and IR morphine tablets.
  - Manipulation of ER and IR morphine tablets resulted in substantial or complete powdering, as rated subjectively using terms such as, but not limited to, "completely powdered", "substantial powdering", or "chunks and partial powdering", whereas manipulation of EG-001 tablets resulted in the following characterizations: "remained intact", "some flaking", and "mostly chunks and flaking."

Duration of Manipulation

- EG-001 100-mg and 60-mg tablets withstood 300 seconds (maximum of test) of manipulation with the food grater, foot file, and razor blade (preselected tools; **Figure 3**).
  - In contrast, the mean duration of manipulation with these tools for IR morphine tablets and ER morphine tablets ranged from 65.5–175.8 seconds and 49.3–163.0 seconds, respectively.

Figure 3. Mean Duration of the Manipulation*



ER=extended release; IR=immediate release.
*Values are the mean (SD) of the duration of the manipulation, with a maximum of 300 sec or until no further reduction in size was achieved.

Conclusions

- **The ALERRT VASs for each of 10 tools showed that the work required and the levels of effort needed to manipulate EG-001 tablets were significantly greater than those needed to manipulate ER and IR morphine tablets.**
- **In contrast to manipulation of ER and IR morphine tablets, which readily powdered, manipulations of EG-001 did not produce much powdered material because of much greater resistance to particle size reduction.**
- **Maximal duration (300 seconds) of effort was needed for manipulation of EG-001 tablets.**
- **The relative hardness of EG-001 tablets, level of effort to manipulate, and limited reduction in particle size after extreme work are expected to offer substantial resistance to abuse for EG-001 compared to other non-AD opioid products.**

References

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Conflicts of Interest
Edward J. Cone and August R. Buchhalter are employees of **Pinney**Associates and provide consulting services to Egalet.

Karsten Lindhardt, Torben Elhauge, and Jeffrey M. Dayno are employees of Egalet and may own Egalet stock or stock options.

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