In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Final Study Report
Control: Non-Interventional.

Title:	Can social listening data be used to provide meaningful insights into abuse or inappropriate use of bupropion? (A feasibility analysis)
Phase:	IV
Compound Number:	GR67205
Effective Date:	12-Dec-2014
Description:	Social listening, specifically in two websites designed for discussion of non-medical use and harm reduction with drugs, was used to evaluate possible abuse and misuse of bupropion as a feasibility project for this data source.

Subject: Drug abuse in relation to drug safety

Author(s): [redacted]

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

PASS INFORMATION

Title	**Can social listening data be used to provide meaningful insights into potential abuse or inappropriate use of bupropion? (A feasibility analysis)**
Version identifier of the final study report	01
Date of last version of the final study report.	n/a
EU PAS register number	202115
Active substance	GR67205
Medicinal product	Wellbutrin™, Wellbutrin XL™, Wellbutrin SR™, Zyban™; also Amitriptyline, Venlafaxine, Oxycodone, Methylphenidate, Alprazolam, Buprenorphine
Product reference	GR67205
Procedure number	n/a
Marketing authorisation holder(s)	Glaxo Wellcome UK Stockley Park West Uxbridge Middlesex UB11 1BT
Joint PASS	No
Research question and objectives	**Can social listening data be used to provide meaningful insights into potential abuse or inappropriate use of bupropion?** Objectives: 1. To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities

	2. To explore the utility of three internet forums to identify cases of interest 3. To describe and characterize the posts of interest (POI) identified during this feasibility analysis (POI is a term coined to denote a user post that may be relevant to drug abuse or inappropriate use of the product in question)
Country(-ies) of study	Worldwide (internet data from English-speaking sites, from much of which no geographic data will be available)
Author	[redacted] MD, RPh, FACOG [redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Glaxo Wellcome UK Stockley Park West Uxbridge Middlesex UB11 1BT UK
MAH contact person	[redacted] contracting safety physician on behalf of GSK

SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study eTrack 202115.

Name of Project Officer: [redacted]

Title of Project Officer: Contracting Safety Physician, GCSP

Signature: _____

Date: _____

Name of Therapy Area Head: [redacted]

Title of Therapy Area Head: VP and Head, Safety Evaluation and Risk Management, Mature Products

Signature: _____

Date: _____

INVESTIGATOR SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge Study eTrack 202115 was carried out as described in this GlaxoSmithKline Report

Name of Investigator: [redacted]

Affiliation: [redacted]

Signature of Investigator: _____

Date: _____

TABLE OF CONTENTS

PAGE

1 ABSTRACT

Title: Can social listening data be used to provide meaningful insights into abuse or inappropriate use of bupropion? (A feasibility analysis):

Q12015

[redacted]

Keywords: bupropion, drug abuse, drug misuse, social media, antidepressants

Rationale and background:

Purpose: to determine the feasibility of using social media for collecting meaningful insights into potential abuse or inappropriate use of bupropion.

Rationale: From proof of concept evaluations for Project CRaWL (Contextualizing Real World drug use through social Listening), we know that information about abuse or inappropriate use potential of marketed GSK drugs is available through social listening (the process of identifying and assessing what is being said about a company, individual, product or brand on the Internet). The quality and quantity of those data are not fully explored at this time or in any formal evaluation setting.

These data are typically quite scant in the standard tools used for pharmacovigilance (spontaneous adverse event reporting, observational databases, and literature reports) as abusers are unlikely to report adverse events or means of abuse to regulatory authorities or often even their personal physician. In a review of data (2004 – 2011) from the Drug Abuse Warning Network (DAWN) database, it was reported that, "There are several limitations to the data used in the study, which preclude the ability to make strong recommendations as to the abuse potential of bupropion." [Bibeau] The data, however, did not provide evidence that abuse of bupropion was growing at that time.

Knowing that there are some data available from online forums and even mainstream social media sites, we believe that further exploration of these may be useful. In this feasibility study for bupropion as an example drug, we hoped to describe the best use of the data collection tool that we are using through a partnership with Epidemico™, an informatics company with interest and experience in this realm.

Background

Bupropion hydrochloride was first approved in the US in December of 1985 and is currently approved in 80 countries, for depression, smoking cessation, and for seasonal affective disorder. Most evidence suggests it has low abuse potential in humans. [Miller, 1983; Griffith, 1983; Rush, 1998; Zernig, 2004].

Abuse of bupropion has been described in published case reports, however, and was first recognized in the setting of correctional institutions where illicit drugs are less available and where bupropion may be widely ordered as a smoking cessation therapy for prison inmates. Most of these reports involve routes other than oral use (the only approved route of administration) including nasal insufflations and intravenous injection [Kim, 2010; Barribeau, 2013; Hilliard, 2013; Reeves, 2013;

Yoon, 2013]. During a recent search of the DAWN database there was a paucity of data on route of administration or confirmation of psychoactive effects [Bibeau]. This is one potential area where social listening data may help significantly augment the existing sources of information that we have on bupropion's abuse or inappropriate use potential.

Research question and objectives:

- To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities
- To explore the utility of three internet forums to identify cases of interest
- To describe and characterize the posts of interest (POI) identified during this feasibility analysis

Study design:

This was a retrospective descriptive observational study, analyzing all available data collected on bupropion and comparator drugs (venlafaxine and amitriptyline) from two internet forums (the third planned forum was unavailable) known to be rich with drug abuse data. Summary statistics on numbers of posts for drugs of known high abuse potential were also provided for contextualization of the bupropion and comparator data.

Setting:

Two online forums focused on non-medical use and harm reduction with drugs: bluelight.org and opiophile.org

Data were collected from publicly available social media or internet forum posts from individuals who chose to post on these sites by Epidemico™ through the DataSift™ platform or directly from the in-scope website administrators. The population was thus self-selecting and voluntary, and included users from any country or background as long as they posted in the English language and agree to the site's policies.

Subjects and study size, including dropouts:

- A total of 7,270 posts were reviewed, containing 7,756 total unique drug references (UDRs, a term used to denote when a single post referenced more than one in-scope drug) of the three in-scope drugs bupropion, amitriptyline, and venlafaxine. Bupropion accounted for 3,472 (45%) of those.
- Of these, 668 UDRs (9%) referenced abuse or misuse of the drug, with bupropion accounting for 438 (13% of the total 3,472 bupropion posts and 66% of the total abuse/misuse-related posts).
- Of note, due to protection of possible personally identifiable information (PII) within the dataset, the number of individual authors accounting for these posts is unavailable or potential abusers/misusers of the drugs in the dataset is unavailable.

Variables and data sources:

- Posts gathered from launch of two online forums in 1997 and 2003 to 29 July 2015.
- Number of posts of interest (POI), a term coined to denote a post that describes or is related to the abuse or inappropriate use of a drug in question, identified over the study period:

Table 1. Number of posts of interest per product

Post of Interest Type	Number of UDRs	% of 7,756 total UDRs	Number Bupropion UDRs	Number Amitriptyline UDRs	Number of Venlafaxine UDRs
Abuse	425	5.5%	305	60	60
Misuse*	243	3.1%	133	40	70
Discussing/experiencing withdrawal from in-scope drug	551	7.1%	67	30	454†
Discussing/using in-scope drug to attenuate withdrawal of another drug	209	2.7%	125	31	53
Discussing/utilizing in-scope drug to 'come down' from a high	11	<1%	6	5	0
Avoiding/discussing drug interactions with in-scope drug	1,497	19.3	690	173	634

*If a post contained both an abuse and misuse UDR, it was captured as abuse.
† Venlafaxine has known 'withdrawal syndrome' that is described in the label, which may explain the high number of posts in this withdrawal category.

- **Table 2. Demographic data (not commonly provided): age, gender, geographic location, education level/occupation, race/ethnicity**

Demographic Variable	Number of UDRs (% of *total abuse/misuse UDRs*, N = 668)
Age group (19 adult, 11 child ≤ 18 years)	30 (4%)
Gender (19 male, 9 female)	28 (4%)
Country (US 5, UK 3, Canada 3, France 2)	13 (2%)
Ethnicity	0 (0%)
Socioeconomic Status Indicators (mostly references to being employed or in school)	15 (2%)

- Number of total posts needed to identify a POI:
    - For abuse/misuse only: 668 UDRs in 7,756 total reviewed = 1 POI per 12 posts reviewed.
    - For all POI as above: 668 abuse/misuse + 551 withdrawal + 209 attenuating withdrawal + 11 'come down' from high + 1,497 interactions = 2,936 total POI UDRs in 7,756 total reviewed = 1 POI per 2.6 UDRs
- Site-specific and population-specific results of above endpoints—Given that only 64 posts (<1%) for the in-scope products came from Opiophile, and the relatively scant amount of demographic information available as above, planned site-specific and population-specific results were not analyzed.

- To better contextualize the overall numbers of these posts, the numbers of posts for drugs of known high abuse potential[2] were also requested and are available for comparison in Table 3.

Table 3: Total numbers* of posts for seven different drugs

Product	Bluelight	Opiophile	TOTAL
Bupropion	4,058	39	4,097
Amitriptyline	1,183	6	1,189
Venlafaxine	3,508	19	3,527
Methylphenidate	12,274	95	12,369
Alprazolam	41,334	835	42,169
Buprenorphine	44,639	1,538	46,177
Oxycodone	104,270	2,269	106,539

* Total numbers before any deduplication or manual review of posts; thus different from the final product numbers for in-scope products presented above for the most appropriate comparisons to be made.

- Calculation of bupropion exposure data and abuse rates from IMS sales data
    - The cumulative postmarketing exposure to bupropion since launch (using IMS data from 1991 to 1997 and GSK sales data since 1998) is approximately 134,161,362 patient exposures up to 31 December 2015.

    - Bupropion total abuse/misuse UDRs per exposure over time thus calculated as 438 mentions per 134,161,362 patient exposures, giving 1 abuse mention in the data source per 306,304 known patient exposures worldwide since 1991. This number is included here as it has been suggested that such data may be used to watch trends over time in FDA draft guidance documents ([FDA], see also section 6.1). Such numbers must be interpreted carefully. It is based on data from only two websites since 1997 at earliest for numerator, while worldwide data for sales since 1991 are used as the denominator (see also section 9.6.1, Limitations).

Results:

Table 4. Posts encouraging vs. discouraging drug abuse

	Bupropion UDRs (% of *bupropion UDRs*, N=438)	**Amitriptyline UDRs (% of *amitriptyline UDRs*, N=100)**	**Venlafaxine UDRs (% of *venlafaxine UDRs*, N=130)**	**Total UDRs (% of *total abuse/misuse UDRs*, N=668)**
Abuse-encouraging	54 (12%)	10 (10%)	14 (11%)	78 (12%)
Abuse-discouraging	178 (41%)	22 (22%)	24 (18%)	224 (34%)
Neither abuse-discouraging or encouraging	68 (16%)	19 (19%)	28 (22%)	115 (17%)
Total	300 (68%)	51 (51%)	66 (51%)	417 (62%)

Table 5. Route of administration information details*

	Bupropion UDRs (% *total routes known for bupropion*, N = 182)	**Amitriptyline UDRs (% *total routes known for amitriptyline*, N = 17)**	**Venlafaxine UDRs (%*total routes known for venlafaxine*, N = 15)**	**Total UDRs (% *total UDRs where route known**, N = 214)**
Route of administration known— Total	182 (42%)	17 (17%)	15 (12%)	214
Intravenous	39 (21%)	5 (29%)	0	44 (24%)
Injection, NOS	15 (8%)	0	0	15 (8%)
Nasal	116 (64%)	5 (29%)	5 (33%)	126 (69%)
Oral- Chewed	1 (1%)	3 (18%)	1 (7%)	5 (2%)
Oral- Swallowed and NOS	16 (9%)	4 (24%)	7 (47%)	27 (14%)
Smoking	1 (1%)	0	0	1 (0%)
Other route (plugging, rectal, parachuting, foiling, "abusing any other way")	8(4%)	0	2 (13%)	10 (5%)

* Some percentages may equal > 100 due to more than one route being discussed in 21 bupropion posts.

Table 6. Procurement information details

	Bupropion procurement method UDRs (% total bupropion *procurement UDRs*)	**Amitriptyline procurement method UDRs (% total amitriptyline *procurement UDRs*)**	**Venlafaxine procurement method UDRs (% total venlafaxine *procurement UDRs*)**	**Total procurement method UDRs (% total *procurement UDRs*)**
Procurement method known— Total	38 (9% of *bupropion total UDRs*, N=438)	13 (13% of *amitriptyline total UDRs*, N=100)	11 (8% of *venlafaxine total UDRs*, N=130)	62 (9% of *total drug UDRs*, N=668)
Illegal purchase	0	1 (8%)	0	1 (0%)
Obtained or stolen from a third party	7 (18%)	7 (54%)	2 (18%)	16 (27%)
Prescribed	29 (76%)	5 (38%)	7 (64%)	41 (66%)
Other ("came across", "found on ground", "by accident"/ implied pharmacy dispensing error)	2 (5%)	0	2 (18%)	4 (6%)

Table 7. Desired effect information details*

	Bupropion desired effect UDRs (% *desired effect known* bupropion)	**Amitriptyline desired effect UDRs (% *desired effect known* amitriptyline)**	**Venlafaxine desired effect UDRs (% *desired effect known* venlafaxine)**	**Total desired effect UDRs (% total *desired effect known*)**
Desired effect apparent (sedative, stimulant, other dissociative effects, unspecified "high")- Total	162 (37% of *all bupropion* UDRs, N=438)	55 (55% of *all amitriptyline* UDRs, N=100)	49 (38% of *all venlafaxine* UDRs, N=130)	266 (40% of *all drug* UDRs, N=668)
Sedative ("downer")	1 (1%)	20 (36%)	1 (2%)	22 (8%)

Stimulant ("upper")	74 (45%)	2 (4%)	7 (14%)	83 (31%)
Other Dissociative/All-arounder	15 (9%)	3 (5%)	14 (29%)	32 (12%)
Unspecified High	54 (33%)	9 (16%)	10 (20%)	73 (27%)
Other	17 (10%)	21 (38%)	14 (29%)	52 (20%)
None	1 (1%)	0	3 (6%)	4 (2%)

* See also section 9.8.1.4—manual curators were trained to capture the "desired effect" whether or not it was apparent that the effect was actually achieved

Table 8. Drugs combined for abuse

	Bupropion drugs combined UDRs (% of *total bupropion UDRs*, N=438)	**Amitriptyline drugs combined UDRs (% of *total amitriptyline UDRs*, N=100)**	**Venlafaxine drugs combined UDRs (% of *total venlafaxine UDRs*, N=130)**	**Total UDRs (% of *total abuse/misuse UDRs*, N=668)**
Drugs combined for abuse	72 (16%)	40 (40%)	27 (21%)	139 (21%)

Table 9. Discussion of magnitude of abuse/misuse problem within the community

	Bupropion community mention UDRs (% of *total bupropion UDRs*, N=438)	**Amitriptyline community mention UDRs (% of *total amitriptyline UDRs*, N=100)**	**Venlafaxine community mention UDRs (% of *total venlafaxine UDRs*, N=130)**	**Total UDRs (% of *total abuse/misuse UDRs*, N=668)**
Discussion of magnitude of abuse/misuse within community (see Figure 8)	112 (26%)	17 (17%)	11 (8%)	140 (21%)

Table 10. Discussion of drug use within the criminal justice system

	Bupropion criminal justice system UDRs (% of *bupropion UDRs*, N=438)	**Amitriptyline criminal justice system UDRs (% of *total amitriptyline UDRs*, N=100)**	**Venlafaxine criminal justice system UDRs (% of *total venlafaxine UDRs*, N=130)**	**Total UDRs (% of *total abuse/misuse UDRs*, N=668)**
Discussion of use within the criminal justice system (see Figure 9)	19 (4%)	4 (4%)	0	23 (3%)

Table 11. Dosage and length of usage information

	Bupropion dosage/length of use UDRs (% of *total bupropion UDRs*, N=438)	**Amitriptyline dosage/length of use UDRs (% of *total amitriptyline UDRs*, N=100)**	**Venlafaxine dosage/length of use UDRs (% of *total venlafaxine UDRs*, N=130)**	**Total UDRs (% of *total abuse/misuse UDRs*, N=668)**
Dosage information known (See Figure 10)	123 (28%)	35 (35%)	31 (24%)	189 (28%)
Length of dosing known (See Figure 10)	56 (13%)	10 (10%)	19 (15%)	85 (13%)

Table 12. Withdrawal experience post results

	Number of UDRs	% of *total withdrawal UDRs* (N=551)	*% of total in-scope drug UDRs**	% of *total drug UDRs*[†]
Bupropion	67	12%	5%	2%
Amitriptyline	30	5%	9%	3%
Venlafaxine[††]	454	82%	35%	14%

* N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

[†] N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

[††] Venlafaxine has labelled known 'withdrawal syndrome'[3] that is described in the label, which may explain the high number of posts in this withdrawal category.

Table 13. Use for attenuation of withdrawal from other drugs results

	Number of UDRs	% of *total attenuation UDRs* (N=209)	% of *total in-scope drug UDRs**	% of *total drug UDRs*†
Bupropion	125	60%	9%	4%
Amitriptyline	31	15%	9%	3%
Venlafaxine	53	25%	4%	2%

* N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

†N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

Table 14. Use to "come down" from a high results

	Number of UDRs	% of *total 'come down' UDRs* (N=11)	% *of total in-scope drug UDRs**	% *of total drug UDRs*†
Bupropion	6	55%	< 1%	< 1%
Amitriptyline	5	45%	2%	< 1%
Venlafaxine	0	N/A	N/A	N/A

* N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

† N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

Table 15. Discussing/avoiding drug interactions with in-scope drug*

	Number of UDRs	% of *total interaction UDRs* (N=1,497)	% of *total in-scope drug UDRs*†	% of *total drug UDRs*††
Bupropion	690	46%	52%	20%
Amitriptyline	173	12%	51%	16%
Venlafaxine	634	42%	49%	20%

* Often drug interaction posts were describing misuse as defined by the FDA and utilized for this review. These posts were captured as 'misuse' and not in this section, as in several examples where the author refers to skipping doses of a prescribed drug in order to get high off of another drug.

† N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

††N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

Discussion

Drug abuse/misuse has been difficult to capture using traditional sources of pharmacovigilance information. The objectives of this feasibility study were to assess the utility of screening social media content as a source of supplementary pharmacovigilance information on drug abuse/misuse. The study, which screened information from two online discussion forums dedicated to recreational drug use and harm reduction, detected some entries related to bupropion, including detailed text descriptions of abuse/misuse experiences. The conclusion from the feasibility study was that these data may be a useful source of information in the future. It was outside the scope of this feasibility study to draw conclusions about the prevalence or health consequences of abuse/ misuse of bupropion from mentions of abuse/misuse on these two online discussion forums.

Statistical Methods

All results were calculated using mathematical totals, percentages, means, and medians. MS Excel 2007 was used to aid in this process. Metrics of inter-rater agreement were calculated in order assess the curation team's agreement on tagging of posts. A random sample of 10 posts were gathered from the dataset and evaluated by all members of the curation team using the same questions and response options available in the manual curation interface. Agreement between curator-applied tags was then evaluated by calculating Fleiss' kappa metrics of inter-rater agreement [Landis]. The use of Fleiss' kappa was justified by the number of raters being assessed (11) and the nominal-scale format of ratings that were applied. The analyses included responses to the first two questions in the curation protocol, which asked curators to identify whether the post included reference to misuse or nonmedical use of in-scope products, and what type of reference was made where applicable. Additional questions were omitted from analysis in order to reflect the curation protocol instruction to leave default answers unchanged if relevant information was not present in each post, and thereby to prevent artificial inflation of inter-rater agreement.

2 LIST OF ABBREVIATIONS

AE	Adverse Event
API	Application Programming Interfaces
BZP	Benzylpiperazine
CNS	Central Nervous System
CRaWL	Contextualizing ReAl World use of drugs through social Listening, a project sponsored by the Pharmacovigilance Centre of Innovation
CSD	Central Safety Department
DAWN	Drug Abuse Warning Network
DXM	Dextromethorphan
EMA	European Medicines Agency
ER	Emergency Room
FDA	(US Federal) Food and Drug Administration
GCSP	Global Clinical Safety and Pharmacovigilance (GSK)
GRA	Global Regulatory Affairs (GSK)
GSK	GlaxoSmithKline

HCPs	Health Care Professionals
IMS Health	Formerly known as Intercontinental Marketing Services
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MTF	Monitoring the Future
NSDUH	National Survey on Drug Use and Health
OCEANS	Operating Companies Event Accession & Notification System
OCMO	Office of the Chief Medical Officer (GSK)
PII	Personally Identifiable Information
POI	"Post of interest", a term coined to denote a user post that may be relevant to drug abuse or inappropriate use of the product in question
RSS Feeds	Rich site summary feeds
SMQ	Standardised MedDRA Query
SRT	Safety Review Team (GSK)
TEDS	Treatment Episode Data Set
THC	Tetrahydrocannabinol
UDR	Unique Drug Reference, used to denote a post that contains reference to more than one in-scope drug
UK	United Kingdom
US/USA	United States of America

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Efexor
Endep
Elavil
Amitrip

3 INVESTIGATORS

[redacted]

4 OTHER RESPONSIBLE PARTIES

[redacted] (Epidemico); [redacted] (Bluelight); [redacted] (Bluelight); [redacted] (Epidemico); [redacted] (Epidemico); [redacted]

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	*30 May 2015*	*31 July 2015*	*Could not confirm authorization from one data source*
End of data collection	*30 July 2015*	*14 Sept 2015*	*Same as above*
Registration in the EU PAS register	*20 Jan 2015*	*20 Jan 2015*	
Final report of study results	*30 May 2016*	*3 June 2016*	*International signature needed on final report*

6 RATIONALE AND BACKGROUND

6.1 Background

Abuse potential, as defined in FDA's draft guidance document for Assessment of Abuse Potential of Drugs [FDA, 2010], refers to a drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces. These drugs are characterized by their central nervous system (CNS) activity. Examples of the psychoactive effects they produced include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. Drugs with abuse potential often (but not always) produce psychic or physical dependence and may lead to the disorder of *addiction.* The concept of *abuse potential* encompasses all the properties of a drug, including, for example, chemical, pharmacological, and pharmacokinetic characteristics, as well as fads in usage and diversion history.

Specifically, the FDA states in the draft guidance that, "sponsors should search publicly available databases, including the Drug Abuse Warning Network (DAWN), the National Survey on Drug Use and Health (NSDUH), the Treatment Episode Data Set (TEDS), Monitoring the Future (MTF), and *other databases* [emphasis protocol author's], to characterize and monitor risks associated with the misuses and abuse of a drug and to estimate the extent of use and abuse of a particular drug."

The draft guidance also includes suggestions for collecting information on the type of data that might be collected for a product (e.g. abuse or inappropriate use events as "numerator" and amount of drug produced in the same time period as "denominator") that could be compared with information on pharmacologically similar drugs. The FDA also suggests that such data could be used to evaluate trends over time.

Background on bupropion abuse potential:

In early preclinical studies, bupropion showed amphetamine-like effects in animals. Drug discrimination studies in rodents and primates indicate that the subjective experience (stimulus cue) elicited by bupropion is generalized to stimulants such as d-amphetamine, cocaine, and methylphenidate [de la Garza, 1987; Bergman, 1989; Kamien, 1989; Lamb, 1990].

Despite the evidence for stimulant effects in animals, suggesting a relevant abuse or inappropriate use potential, several clinical studies in humans indicated that oral intake of bupropion had lower abuse liability than amphetamine, methylphenidate, and even caffeine. Accordingly, it was concluded that bupropion did not exhibit amphetamine-like characteristics in humans, and most evidence suggests it has low abuse potential in humans. [Miller, 1983; Griffith 1983; Rush, 1998; Zernig, 2004].

Abuse potential had been part of the Benefit Risk Management Plan for bupropion up until 2003 and at that point, had no longer been regarded as a potential risk that required additional/further evaluation outside standard pharmacovigilance monitoring. Routine pharmacovigilance monitoring during 2013 identified an increase in the number of spontaneous reports of bupropion abuse in the GSK worldwide safety database (OCEANS). Bupropion is only licensed for oral administration. The reports of abuse described inhalation or injection of crushed tablets with adverse reactions including seizures or death. The company's global datasheet was updated in early 2014 with a warning that inappropriate routes of administration may lead to a faster absorption (potential overdose) and that seizures or death have been reported.

Background on Social Listening and the Safety Listening Lab

Currently, post-marketing safety surveillance relies on data from spontaneous adverse event reports, published literature and observational databases (medical records, insurance claims). These data sources have limitations that include: significant under-reporting (some estimate that less than 10% of adverse events are reported), lack of geographically diverse data (most data come from the United States and Europe), and time lag (most data sources lag 9-12 months).

One potential new source of drug safety data may be social media. A recent survey showed that nearly 90% of the U.S. adult population uses the internet, and 72% of those users have searched online for information about health issues [Pew]. Furthermore, between 3% and 4% of internet users have posted about their experiences with health care service providers or treatments on social media sites [Pew]. Much of the data posted by these patients are publicly available on the internet, depending on the individual's use of privacy settings when posting.

Because the internet is already being used to communicate medical information, social listening, the act of monitoring public conversations on the internet to better inform the branding and understanding of a product [Nair], is worthy of further exploration for several reasons. First, it may unlock a rich data source that has been previously untapped for pharmacovigilance. Second, it introduces the voice of the patient directly into the conversation about drug safety, using his or her own words, which may prove valuable to the understanding of real-world medication use. Third, the worldwide utilization of social

media and rapid availability of data may offer real-time access to geographically diverse data without a significance temporal lag between an event happening and it being discovered by the PV community. Fourth, patients may be more willing to discuss symptoms that might be considered embarrassing or behaviours that might be illegal or taboo in a relatively anonymized forum on the internet. These social listening attributes would potentially help overcome some of the limitations of other data sources.

This led GSK's Central Safety Department (CSD) to design this study to ascertain whether some of the power of social media could be harnessed for the purpose of monitoring a historically difficult-to-monitor area (nonmedical drug use). The application of this tool to evaluate abuse concerns in medications for which GSK is actively seeking new data sources was one of the first projects of the Safety Listening Lab, as described in the original protocol.

6.2 Rationale

Although the numbers of abuse reports are small relative to the total number of reports for bupropion in the safety database (OCEANS), there was sufficient info to warrant investigation of the potential effect on public health. PRJ2215 was performed to evaluate abuse or misuse of bupropion by off label routes of administration in the DAWN database (2004 – 2011). There were several limitations to the data used in the study, which precluded the ability to make strong recommendations as to the abuse potential of bupropion. However, the data from this study "did not provide evidence that abuse and misuse of bupropion is growing." [Bibeau] Social media listening was identified as a data source that could potentially provide a better understanding of bupropion abuse potential.

7 RESEARCH QUESTION AND OBJECTIVES

QUESTION: **Can social listening data be used to provide meaningful insights into potential abuse or inappropriate use of bupropion? (A feasibility analysis)**

Purpose

- The purpose of this analysis was to determine the feasibility of using social media for collecting meaningful insights into potential abuse or inappropriate use of bupropion.

Objectives and Endpoints

Objectives	Measured Outcomes
• To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities	• Number of posts of interest (POI)* identified over a period of time • Total number of posts that must be reviewed in order to identify each POI* • Describe indicator scores for POI* vs. non-interest posts (not completed in this initial feasibility study; perhaps for future development)
• To explore the utility of three internet forums to identify cases of interest	• Site-specific results of above endpoints • Population-specific results of above endpoints (See Sections 9.8.2 and 10.8, not reported due to low numbers in actual dataset)
• To describe and characterize the posts of interest (POI) identified during this feasibility analysis	• Descriptive data

*POI (post of interest) is a post that describes or is related to the abuse or inappropriate use of bupropion. At the end of the study, this was defined as clear misuse or abuse, as well as discussing one or more of the four categories listed in section 10.6. Of note, posts were reviewed manually by reviewers blinded to site/source in order to guard against introduction of bias.

8 AMENDMENTS AND UPDATES

No.	Date	Section of study protocol	Amendment or update	Reason
1	*31 Mar 2015*	*4,6,7,9*	Prospective data collection changed to retrospective	Learned from direct contact with sites that retrospective data are available and would lead to quicker results
			In-scope websites changed and thus wording of objective # 2 changed	Initial data from planned websites offered no new insights
			Project CRaWL team name changed to Safety Listening Lab	Project CRaWL concluded, led to creation of Safety Listening Lab March 2015
			Comparator drug handling changed	Increasing experience with resources needed for manual curation led team to feel more strongly about focusing on unanswered questions and not re-visiting abuse potential of drugs of known high potential
			No longer focusing only on possible Proto-AEs, but curating all posts	Very little data on performance of the automated classifier in this realm led to team concerns about missing valuable information by relying on the classifier tool to filter the data for us
			Variable for collection added: Mention of magnitude of the abuse problem within the community	From Section 9.6.1 below. After initial data exploration, new data points may need to be added in order to record unforeseen points.
2	*n/a*			

9 RESEARCH METHODS

9.1 Study design

This was a non-traditional feasibility study design using a novel data source in collaboration with the informatics company Epidemico™ to apply to pharmacovigilance. The design was essentially a retrospective descriptive observational study. Data were collected retrospectively from internet websites and forums where drug abuse or inappropriate use may be discussed and voluntarily posted on a public site. Data were collected on chatter concerning bupropion, as well as other drugs that are known to have lower or similar abuse potentials to bupropion (venlafaxine and amitriptyline, see section 9.1.1 for further information). Summary statistics on numbers of posts concerning drugs of known high abuse potential (oxycodone, buprenorphine, methylphenidate, and alprazolam) were also reported to help contextualize the data.

9.1.1 Product and Comparator Selection

9.1.1.1 Bupropion

Bupropion increases the intra-synaptic concentrations of norepinephrine and dopamine via dual inhibition of the reuptake of these neurotransmitters [Stahl]. In mouse models, bupropion has shown increased extracellular dopamine and norepinephrine concentrations in the nucleus accumbens, which houses the brain reward system in the development of addiction [Stahl, Nomikos]. Bupropion is approved by the US FDA for the treatment of major depressive disorder and for the treatment of nicotine dependence as an aid to smoking cessation [Wellbutrin USPI, Zyban USPI]. The pharmacokinetics are described with oral administration only and oral bupropion exhibits extensive first-pass metabolism in the liver [Wellbutrin USPI]. Crushing and snorting as well as intravenous administration will bypass this metabolism, allowing for a more rapid and significant rise in plasma concentrations, which could theoretically result in euphoria [Evans]. Subjective, yet non-standardized, effects reported in literature indicate a cocaine-like high, stimulant high and euphoric effects [Reeves, Yoon, Vento, Baribeau].

9.1.1.2 Amitriptyline

Amitriptyline is in the tricyclic antidepressant (TCA) class of drugs and is approved by the US FDA for the relief of symptoms of depressive illness [Elavil monograph]. Amitriptyline inhibits the reuptake of norepinephrine and serotonin in adrenergic and serotonergic neurons and also blocks muscarinic and histamine receptors [Elavil monograph, Hepburn]. The exact mechanism of action in treating depression and the pharmacologic basis for nonmedical use is unknown [Elavil monograph]. There are discussions in the literature regarding nonmedical use of amitriptyline, including case reports and surveys [Delisle, Wohlreich, Hepburn, Prahlow, Peles, Cohen 1978, Shenouda]. The majority of TCA misuse case reports in the literature do not identify the route of administration. When reported, the medications were described as taken orally, and in some cases in large doses to produce a ‘high’ euphoria, and ‘buzzed and numbed up’ and ‘pleasant, more sociable’ feeling [Evans, Shenouda, Wohlreich].

9.1.1.3 Venlafaxine

Venlafaxine is in the serotonin and norepinephrine reuptake inhibitor (SNRI) class of drugs. The exact mechanism of venlafaxine antidepressant action is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central

nervous system, through inhibition of their reuptake [Ellingrod, Effexor USPI]. Venlafaxine is approved by the FDA for major depressive disorder, generalized anxiety disorder, social anxiety disorder and panic disorder [Effexor USPI]. There are case reports in the literature that describe large doses of oral ingestion (4,050 mg and up to 3,750 mg/day) to achieve altered states ('amphetamine-like high', 'more empathic and sociable' and 'elated' mood) [Quaglio, Sattar]. These cases suggest that the nonmedical use of SNRIs may result in amphetamine-like effects or the dissociative effects of excess serotonin [Evans].

9.2 Setting

Setting: Public internet forums where drug abuse is discussed, including bluelight.org, and opiophile.org. (Of note, it was not possible to obtain permission from Erowid administrators to use their available data for research purposes and the study thus proceeded with only bluelight and opiophile from the original planned three sites). Posts in the English language were included in the search, and all cumulative posts mentioning bupropion products as well as comparator products (venlafaxine, amitriptyline) were collected.

Data were collected using DataSift™, a commercial social media/Big Data collection and delivery service, and/or in direct cooperation with the website owners. Epidemico™ then provided the commercially available deidentified data to GSK. The medical product data were acquired from publicly available online forums that are accessible through proprietary automated content scraping technology, Application Programming Interfaces (APIs) officially published by the sources/sites, and RSS feeds.

All posts containing references to the products were processed using customized natural language processing to identify formal and vernacular language associated with terms from drug misuse related preferred terms in the English Language MedDRA version 18.0 terminology, including the broad scope Standardised MedDRA Query (SMQ) 'Drug abuse, dependence and withdrawal'. In addition, three Preferred Terms (PTs) outside of this SMQ: Injection, Injection site reaction and Legal problem, were added.

9.3 Subjects

Data were collected from publicly available social media or internet forum posts from individuals who chose to post on Bluelight or Opiophile by Epidemico™ through the DataSift™ platform or directly from the in-scope website administrators. The population was thus self-selecting and voluntary, and included users from any country or background as long as they posted in the English language and agreed to the site's policies.

9.4 Variables

All posts mentioning bupropion products as well as comparators (and common misspellings and slang terms from proprietary [Epidemico™ and Bluelight™] online data gathering technologies) were acquired:

- All posts on the in-scope internet sites were reviewed, as the sites are specifically targeted to chatter concerning abuse or inappropriate use
- All posts were categorized in to:
    - Abuse- or misuse- related

- Otherwise meaningful mention (see "Other analyses: posts of interest outside of abuse/misuse", Section 10.6)
- Unclear/uncodable or spam

The manually curated bupropion abuse-related posts were then described in the following settings. Individual POI are presented in one or more categories described below as appropriate:

- Route of Administration –Reviewers noted if the following were mentioned:
  - Nasal insufflations (e.g., snorting)
  - Oral- chew
  - Oral- swallow
  - Smoking
  - Intravenous
  - Injection
  - Subcutaneous
  - Ambiguous and other routes of administration – internet jargon (during initial feasibility project, the possibility of further differentiation amongst routes of administration was not apparent, although there were some "other" routes noted, including "parachuting (a method of swallowing drugs by rolling or folding powdered or crushed drugs in a piece of toilet paper to ingest while avoiding the taste of the chemical, "foiling" (heating a drug on foil and inhaling its vapours)", and "plugging"/rectal administration)

- Dosage and length of use

- Categorization of euphoric effect – for all posts identified as abuse-related, the nature of the high was broadly characterized as being (example terms that would be mapped to the characterizations follow each term) [Cohen 2011]:
  - Stimulant-like ("upper")—CNS stimulation, insomnia, energy/energized, increased heart rate, decreased appetite, seizures, increased confidence, excitement, rush, nervousness, anxiety, anger, euphoria
  - CNS Sedative-like ("downer")—sedative, anxiolytic, nerve pill, tranquil/tranquilizer, CNS depression, slowed heart rate, slow respiration, sleep/drowsiness, dull senses, diminished pain, slurred speech, coma, hypnotic
  - Other dissociative effects and hallucination ("all arounder")—psychedelic, distorted perceptions, nausea, dizziness, sweating, raised blood pressure, distorted sensory messages, illusion, altered perception, intensified external stimulus perception, delusions, delirium
  - Unknown or unspecified

- During the early review period, curators decided to also add the following categories upon noting some ambiguity and difficulty in classifying:
    - Unspecified "high", when the "high" terminology was used but it was unclear which of the above categories might be referred to
    - None (signifying that no psychoactive effect was sought by the abuser/misuse)

- Prison/criminal justice flag-- Given the nature of the case reports, any interaction with the criminal justice system (prison, jails), etc. was manually flagged using a dichotomous indicator.

- Procurement comments—drug prescribed for patient, obtained/purchased illegally from street/market, obtained/stolen from family member or other acquaintance

- Polypharmacy: determination of whether or not other substances were ingested simultaneously or in combination with bupropion and other in-scope products

- IMS Sales data
- Demographic information where available: age, gender, geographic location, education level/occupation, and race/ethnicity
- Mention of magnitude of the abuse problem within the community

9.5 Data sources and measurement

See also section 9.2, Setting, and 9.3, Subjects

Data sources were bluelight.org and opiophile.org, two public internet forums where non-medical use of drugs and harm reduction are discussed. Posts in the English language were included in the search, and all posts mentioning bupropion products as well as comparator products (venlafaxine, amitriptyline) were collected. Summary statistics were also collected for comparators of high abuse potential also as noted in section 9.1, Study Design.

Data were collected from the website launch dates (bluelight.org 1997 and opiophile.org 2003) to 29 July 2015.

9.6 Bias

9.6.1 Limitations of the research methods and possible bias introduction determined prior to the data evaluation

The current study was primarily designed to assess the utility of social media in detecting a signal of abuse potential of a product.

There are currently some major limitations in the use of social media information in terms of quantitative signal evaluation where the abuse potential of one product is compared to the abuse potential of another product. These limitations relate to missing information for the numerator and unclear denominators for any comparisons of abuse frequency.

Regarding the numerator, mention frequency is likely to be driven by access to the medication (if relatively low availability/ circulation of a drug, the potential for diversion or misuse will be lower). Although attempts were made to provide some context around the number of bupropion mentions versus other drugs by assessing mentions per exposure using IMS sales data as a proxy for availability/circulation, there are limitations to this approach. Sales data may not be available for all countries and there may be access controls applied to a product in some which will not be reflected in the sales data.

Mention frequency may also be affected by the type of experience resulting from the abuse/misuse. For example, it may be that more dramatic effects/ experiences ("highs" or psychedelic experiences) are mentioned more frequently than effects such as somnolence. If products differ in the type of experience they elicit, comparisons may be biased due to differential potential for missing information in the numerator.

Another possible influence on mention frequency is press or media coverage of a certain drug, or reported celebrity use or overdose of a specific product. These effects have not been quantified, but it is certainly likely that discussions of propofol increased in the weeks to months following Michael Jackson's death from overuse of the drug in the U.S.

The extent of information missing from those who abuse/misuse a substance and do not post about it cannot be evaluated. Furthermore, the demographic profile of those who post about their substance abuse/misuse compared to the profile of those who abuse-misuse substances but don't post is relatively unknown. Validation studies which compare the demographic profile of those who abuse/misuse and post versus those who abuse/misuse a product and don't post are likely to be difficult to conduct given the difficulty in identifying those who abuse/misuse substances and the legal implications involved. If a product that is more likely to be abused/misused by individuals who don't post about their experience is compared to a product that is more likely to be abused/misused by people who do post, then these comparisons will be biased.

Other limitations of studying this novel tool include: difficulty mapping vernacular terminology to standard regulatory dictionaries, ever-changing and evolving nature of vernacular speech, and confounding by spam and advertisement-type posts as well as the imperfect nature of the de-duplication tools for posts.

9.6.2 Further limitations and possible bias introduction determined during the data review

Protecting Personal Identifiable Information (PII) sometimes necessitates losing context of a post, such as when the word "buzz" is deleted from a post due to the possibility of it being a person's first name.

There are multiple definitions of abuse and misuse [Smith 2013]. Due to the regulatory reporting requirements of this study, the team agreed to use the FDA definitions of both abuse and misuse during the manual curation process.

The curation of these data is believed to be accurate (See also Section 9.8.1). Because of the human element involved in manual curation, intra-and inter-rater variability may be present, and accuracy cannot be guaranteed.

9.7 Study size

There were no a priori specified hypotheses for this study to drive sample size calculations. All eligible cases were included from the two available websites, and all cases obtained for bupropion and comparator drugs venlafaxine and amitriptyline were manually curated as planned.

9.8 Data transformation

9.8.1 Manual data curation

Data were collected by Epidemico™ as described above and imported in to the Insight Explorer tool (copyright GSK) for manual curation and database entry. Each post was reviewed individually by at least one trained curator, and the following data attributes were extracted, following the guidelines noted here:

- In general during curation, we chose the *most conservative approach* when there was doubt or a post was ambiguous. If the post was deemed a simple "judgment call" or more than one interpretation could apply, the point in question was left at the DEFAULT value (i.e.--if it wasn't clearly abuse/misuse, then the conservative approach was NOT to tag the post as abuse/misuse)
- Alcohol, marijuana/THC, caffeine and nicotine products were treated the same as any other substance or drug for curation purposes
- When handling these posts, any post characteristics that resided *only* within quoted text from another post were not tagged/selected (to avoid duplication), but the information within the quotes could be used for understanding the *new* text within context.

9.8.1.1 Abuse and misuse definitions

- **Abuse:** The nonmedical use of a drug, repeatedly or even sporadically, for the positive psychoactive effects it produces [FDA 2010] Of note, 'addiction' was not necessarily deemed to mean 'abuse', as someone can be addicted to a prescription product they are not abusing; if a post described addiction that was not clearly abuse or misuse then it was not classified as in-scope.
- **Misuse:** The use of a drug outside label directions or in a way other than prescribed or directed by a health care practitioner. This definition includes patients using a drug for a condition different from that for which the drug is prescribed, patients taking more drug than prescribed or at different dosing intervals, and individuals using a drug not prescribed for them, although for therapeutic purposes [FDA, page 354]
- NOTE: Posts were tagged whether the abuse or misuse was only discussed or actually experienced by the author.

9.8.1.2 Post categorization general questions

Is this an abuse/misuse-related post or other post of interest for an in-scope product?

- Default was "YES" since only posts that contained references to the products associated with terms from drug misuse related preferred terms in the English Language MedDRA version 18.0 terminology, including the broad scope Standardised MedDRA Query (SMQ) 'Drug abuse, dependence and withdrawal', and/or the three Preferred Terms (PTs) 'Injection, Injection site reaction and Legal problem' as noted in section 9.2 .should have been included from Epidemico.
- If changed to "NO", then there was no further input from the curator. This meant the post was not further evaluated for this report although if personally identifiable information (PII) was present it was still tagged and recorded.

What is the category of this post? Options: (see definitions above)

- Abuse
- Misuse-- (If a post could be both abuse *and* misuse, the higher-level term *abuse* was chosen)
  - Note: This included both discussing *and/or* personally experiencing abuse or misuse
  - Note: Typically when a post consisted of simply a list of products that the poster had tried/used, it was marked as "no" for abuse/misuse-related.
- *Only if* the post did *not* fall into the "abuse" or "misuse" definition as above, but was still of interest for one of the following reasons, it was categorized as follows*:
  - Discussing/experiencing withdrawal from in-scope product (even if product was being utilized as prescribed)
  - Discussing/using in-scope product to attenuate withdrawal of another product (this included references to "help with" coming off or otherwise aid in the process)
  - Discussing/utilizing in-scope product to 'come down' from a high
  - Discussing/avoiding drug interactions with in-scope product (even if interaction was with a prescribed product)
  - Other: the post category could be noted in the comments box

  *If one of these 'posts of interest' was assigned, the curation step ended there without further detail extraction.

Exclude post due to spam or advertisement? "YES" was clicked and the post discarded from the dataset entirely only if the post was something that evaded the initial spam filtering. This category was also used when the post was *only* a reposted/copied

and pasted article/news story or other internet post with no additional input from the poster, or in the event that the post was written in a language other than English.

9.8.1.3 Poster and Patient Information curation questions

Patient Age Range

- Entered only if there was evidence to suggest that the patient is "adult, child (<18), or elderly (≥65)"
- Entered only if the *patient*'s (user/consumer of the drug) age was apparent, whether or not they were the post author

Patient Gender

- Entered only if clear. Examples: "He loves his [drug name]", "this gal loves her [drug name]", etc.
- Entered only if the *patient*'s (user or consumer of the drug) gender was apparent, whether or not they were the post author

Poster Location/Set Country

- If any info was available in the "Poster Location" field from background/metadata *or* the post itself (Examples, "I drive in to Philly every day for work, #'Merica", etc.), country was assigned using the following rules:
  - If obvious location, enter the country (Charlotte, NC = USA)
  - If obvious fictional location, skip (Hogwarts, Second Star to the Right, Your Momma's Bedroom…)
  - If in doubt, search it on Google, using "where is _____" in search bar. If first page of Google hits all map to the same place, list the country. If NOT, leave as "unknown". Examples:
    - "Where is RVA" clearly points to Richmond, Virginia
    - "Where is near south downs way" clearly maps to lower UK
    - "Where is the preciado party" brings up unrelated results; leave "unknown"
    - "Where is Kensington" brings up both UK and US locations; leave "unknown"
- Of note, formulations that may be available in a specific region or regions were not considered enough information to assign country

9.8.1.4 Product Information: curation questions for *each* in-scope drug/UDR

Route of administration

- Only chosen if there was a clear route discussed
- Did not assume "took" to mean an oral route necessarily
- For parenteral methods, "injection" was chosen if it was clearly injected but unclear if IV/SQ/IM; IV chosen if the route of administration was clearly intravenous

- Otherwise, best judgment was used but with the general rule of thumb of leaving at default/unknown if there was more than one interpretation that could be made
- If more than one route discussed, this was also noted

Length of Use

- Summative language was used to express what was known from the post (Examples: "I tried it once", or "have been doing this for 2 months now")

Dosage

Verbatim text of what the post author wrote ("2 oxycodone, 4 shots, 2 extra-strength Tylenol") unless there was a specific dosage given (50mg, 25mg). Dosage for bupropion was then further manually reviewed after curation was completed and placed in to uniform numerical dosages where possible for an arithmetical calculation of mean and median dosing mentioned in this report.

Abuse encouraging or discouraging?

- Abuse-Encouraging = positive conversation about abuse experience
- Abuse-Discouraging = negative conversation about abuse
- Neither = neutral conversation about abuse experience (includes mixed feedback, including examples such as "great for sex, *but* not worth it for a high")
- Unknown = not discussed or unclear/indecipherable (default value)

Procurement method

- Illegal purchase
- Obtained/stolen from a third party
- Prescribed by doctor
- Other—comments were used when needed
- Unknown = default
- If more than one method of procurement, this was also noted

Desired Effect

- In general, this section was used to describe the type of effect (or lack thereof) that a poster was trying to achieve by abusing a product or combination of products. See definitions in section 9.4.
- Note the desired effect was captured whether or not it was apparent that the effect was actually achieved by the user
- Unknown/not discussed = default
- Sedative like ("downer")
- Stimulant like ("upper")
- Other dissociative effects and hallucination ("all-arounder")
- Unspecified high = the word "high" used or alluded to without further information

- Other: curator comments could be entered to explain
- If more than one effect desired, this was also captured

Desired effect similar to

- Free text was added here if the abuse or abuse combination was likened to the high of another product--"combining product X and product Y reminds me of cocaine" or was described as NOT being like the high of another product--"I thought combining product X and product Y would be similar to a codeine high, but it wasn't"

Misuse/abuse outcome or effect

Free text was added to describe any non-desired outcome or effect of the abuse/misuse (i.e.: "had a seizure" or "ended up in the ER in a coma after amitriptyline use/overuse"). This was captured whether the outcome was actually experienced *or* theoretical/feared.

9.8.1.5 Other attributes mentioned in the post, as yes/no variables

Contains PII

- PII included but was not limited to: name, address, email address, "handle" or username for internet forums, date of birth, nickname, license plate numbers, telephone number, face, fingerprints, etc…

Socioeconomic status (SES)

- Captured if specific line of work or the presence or absence of employment mentioned *or* other SES indicators present. Examples:
    - Mention of "missed work" or "left work early" or other indication of employment was present
    - Education level mentioned such as "#MedStudentLife" or "I have a PhD and still can't figure out these directions!"
    - Indications of being on government/social assistance or entitlement programs ("I'll just take my Medicaid voucher somewhere ELSE!")
    - Mentions of financial status

Is the post author seeking information?

- If "yes", a brief comment was made for possible future evaluation
- Examples: "Does anyone else have this happen?", "Anyone have any other suggestions? Can I take these two drugs together? ", etc.

Ethnicity: Only if clear by post text or hash tags. Again, no assumptions were acceptable.

Drugs combined for abuse/misuse: Captured if there was mention of how to effectively combine (or avoid doing so) for abuse, for a high or to potentiate the effects of another drug, or discussion of drug 'cocktails' or drug combinations (including illicit drugs) that resulted in a high/other effect when combined with an in-scope product.

Community Mention: Captured in attempt to document the magnitude of the abuse problem with the in-scope product, if post discussed at least 2 people abusing the same product or specifically negated use by others, or any other indication of the size of the abuse problem with the in-scope product.

Happened within criminal justice system? This was captured if the abuse occurred during incarceration or while in custody of criminal justice system.

9.8.2 Data calculations and transformation after curation

Objectives
• To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities
• To explore the utility of three internet forums to identify cases of interest
• To describe and characterize the posts of interest (POI) identified during this feasibility analysis

Objective One: (To determine if social media can identify cases of potential abuse of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities)

Data on all reports of bupropion related to abuse were captured and examined. Data from each post was extracted and descriptive statistics were reported in summary tables and figures (see Tables 17 – 24, Figures 1 – 10, Section 10).

Bupropion results were presented alongside the results of comparator drugs in order to provide some context around frequency of mention and relative public health burden. Formal comparisons of abuse potential across drugs are not possible given the limitations of the data (See also Limitations, Section 11.2). In an effort to adjust for availability/circulation, the number of abuse mentions per exposure was calculated for the target product bupropion using available IMS sales data.

Of note, initial plans called for description of "indicator scores for POI vs. non-interest post" as part of this objective's measured outcomes. This was not completed in this initial feasibility study since it requires an initial dataset for design and completion, and is thus a possibility for future development. See also Section 10.8. Summative graphs were then used for visual data description.

Objective Two: (To explore the utility of three [two in final dataset as noted in Sections 9.2, 10.8] internet forums to identify cases of interest)

Initial measured outcomes called for site-specific results and population-specific results of endpoints. Given that only 64 posts (<1%) for the in-scope products came from Opiophile, and the relatively scant amount of demographic information available as reported in Section 10.3 (Table 17) , planned site-specific and population-specific results were not analyzed.

Objective Three: (To describe and characterize the posts of interest (POI) identified during this feasibility analysis)

Qualitative description of the data was reported. Some example posts were included in the final report to help the audience conceptualize the tool and dataset. For any

illustrative posts included, post text has been paraphrased and/or altered in non-meaningful ways to protect individuals' privacy.

9.9 Statistical methods

9.9.1 Main summary measures

As noted above, no power or sample size calculations were done and no a priori hypotheses were generated for testing. Thus, only arithmetic percentages and basic mean and median calculations were used in analysis and comparison of the data.

9.9.2 Main statistical methods

Metrics of inter-rater agreement were calculated in order assess the curation team's agreement on tagging of posts. A random sample of 10 posts were gathered from the dataset and evaluated by all members of the curation team using the same questions and response options available in the manual curation interface. Agreement between curator-applied tags was then evaluated by calculating Fleiss' kappa metrics of inter-rater agreement [Landis]. The use of Fleiss' kappa was justified by the number of raters being assessed (11) and the nominal-scale format of ratings that were applied. The analyses included responses to the first two questions in the curation protocol, which asked curators to identify whether the post included reference to misuse or nonmedical use of in-scope products, and what type of reference was made where applicable. Additional questions were omitted from analysis in order to reflect the curation protocol instruction to leave default answers unchanged if relevant information was not present in each post, and thereby to prevent artificial inflation of inter-rater agreement.

9.9.3 Missing values

As noted in section 9.7, all posts obtained from the data vendor were included for review.

9.9.4 Sensitivity analyses

None performed, see also 9.9.1 above.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

This was an original design with data collection for a novel purpose via a novel method. There was no prior validation. This was the reason for including the comparator drugs as well as IMS sales data for denominator comparisons, consistent with the FDA's draft guidance document [FDA, 2010].

9.11 Study Management

9.11.1 Ethical approval and subject consent

In this study, we analyzed the archives of two web forums. Two main areas of ethical focus were considered for this work: informed consent from individuals and communities and the protection of PII.

We drew from the heuristic approach provided by McKee and Porter [McKee] that charts two dimensions against each other: private to public communication and sensitive to non-

sensitive information. Content that is deemed sensitive and is in the public domain sits in a grey zone from an ethical perspective, and the extent of protection for the individuals who write the content and the communities that host the content should be assessed on a case-by-case basis. The community discussions demonstrate that contributors are aware of the public nature of the content that they post, and almost all contributors utilize pseudonyms to mask their identities. Although the subject matter may be seen as sensitive, these elements led the research authors to determine that consent from individual contributors was not necessary to conduct the research. It was also important to maintain any particular contributor's anonymity, as the extent to which their pseudonym may reveal identifying information about them is unknown to the researchers. Therefore, to protect the identity of all posters, PII was removed from all posts by a third-party vendor before receipt of the posts for curation. This included screen names, user names, first and last names and addresses. In addition, where posts were included as examples in this paper, the post text has been paraphrased and/or altered in non-meaningful ways to protect poster identity and prevent unmasking using Internet search engines.

Some researchers anonymize the names of the web forums that they utilize as data, to further assure confidentiality of the individual contributors or because the group had not been actively involved in the research, nor given consent to be involved [Daniulaityte (Am J Addictions), Butler 2007]. Here, we took a participatory or partnership approach [Barratt 2010]. Bluelight.org has a research portal accessible from the front page of the website, which asserts Bluelight's ownership of the forum content and instructs researchers to contact Bluelight administrators to discuss proposals for research, including archival analyses. The researchers contacted Bluelight to initiate discussions regarding this project, resulting in a partnership approach involving regular contact and contribution of Bluelight representatives to this paper.

We contacted Opiophile via email to request consent and terms of access for gathering data from that forum. No response was received from Opiophile, so we reviewed the site's Privacy Notice and User Agreement and determined that gathering data for research purposes was within the scope of permitted uses. Opiophile forum posts were gathered using customized web crawling software that stored the primary body of text included in each post. Usernames, post titles, thread titles, or other information allowing retrospective identification of the authors' online identities were not included in the dataset used for curation or analysis.

We contacted a third potential data source, Erowid.org, to request consent and terms of access for gathering samples from their database of user-reported experiences with drugs. No response was received from Erowid, and their Usage Agreement explicitly prohibited data gathering or publishing of analyses without prior permission. In light of those policies and the absence of response from site administrators, Erowid was excluded as a data source for this study.

9.11.2 Subject confidentiality

All data in this study are publicly-available and de-identified as part of Epidemico's standard commercial product offerings prior to being provided to GSK. The study team has worked with patient privacy experts to ensure that this is protected to the best of our ability and any potential concerns have been fed back to Epidemico for continuous quality improvement of the data collection and de-identification system.

9.11.3 Reporting of adverse drug events

During this study, reportable adverse events were not noted due to the nature of the de-identified data. The following governance was in place:

- For the social media listening project, de-identified data were purchased from a third party vendor after being stripped of PII. Therefore, in the absence of an identifiable reporter, there was no individual case reporting requirement. Instead, any signals noted will be reported either in an expedited manner or as part of routine aggregate reports in keeping with how observational data from other sources is currently treated.
- In order to ensure alignment and acceptance both internally and externally, GSK has consulted and communicated this approach with the US Food and Drug Administration (FDA), Medicine and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA), GSK Global Safety Board (GSB), the GSK Office of the Chief Medical Officer (OCMO) Leadership Team, Global Digital Risk Board, the patient privacy office, Pharmacovigilance compliance, regulatory compliance, legal, GSK IT, the joint GSK Global Clinical Safety and Pharmacovigilance (GCSP)/Global Regulatory Affairs (GRA)leadership team, and others.

10 RESULTS

10.1 General notes on results reporting

The authors of this report have found that in order to present the data in the most accurate and meaningful format, total drug-specific posts instead of total UDRs were frequently used as denominators to calculate percentages . Therefore the percentage *denominator* for each graph was noted in *italicized* text and numerically as "N". For example, in Figure 2 which illustrates UDRs that were classified as Abuse vs. Misuse the percentage *of total drug-specific posts* was presented as the denominator for each drug *instead* of total number of UDRs as the denominator across all three drugs. Of note, because of this a taller bar in a graph may show a lower percentage. See Table 16 below for example.

Table 16: Illustration of how changed denominators affect data presentation

	Denominator = total drug specific posts			***Denominator = total number of UDRs for all three drugs***		
	Bupropion N=438 (%)	**Amitriptyline N=100 (%)**	**Venlafaxine N=130 (%)**	**Bupropion N=7756 (%)**	**Amitriptyline N=7756 (%)**	**Venlafaxine N=7756 (%)**
Abuse UDRs	305 (70%)	60 (60%)	60 (46%)	305 (4%)	60 (1%)	60 (1%)
Misuse UDRs	133 (30%)	40 (40%)	70 (54%)	133 (2%)	40 (1%)	70 (1%)

Please also note that Appendix 1 contains **all** of the same data as below, but in tabular format.

For any example posts included, post text has been paraphrased and/or altered in non-meaningful ways to protect individuals' privacy.

10.2 Participants

- A total of 7,270 posts were reviewed, containing 7,756 UDRs of the three in-scope drugs bupropion, amitriptyline, and venlafaxine (some posts referenced more than one drug)
- Due to measures put in place to protect PII in this data source, the number of specific authors of posts is not available.

10.3 Descriptive data

Demographic information from post authors were not commonly provided, as shown in Table 17.

Table 17: Demographic information availability

Demographic Variable	**Number of UDRs (% of *total abuse/misuse UDRs*, N = 668)**
Age group (19 adult, 11 child ≤ 18 years)	30 (4%)
Gender (19 male, 9 female)	28 (4%)
Country (US 5, UK 3, Canada 3, France 2)	13 (2%)
Ethnicity	0 (0%)
Socioeconomic Status Indicators (mostly references to being employed or in school)	15 (2%)

10.4 Outcome data: Drug-specific overview numbers and abuse vs. misuse

Figure 1: Total individual drug UDRs reviewed (% of *total UDRs*, N=7,756)

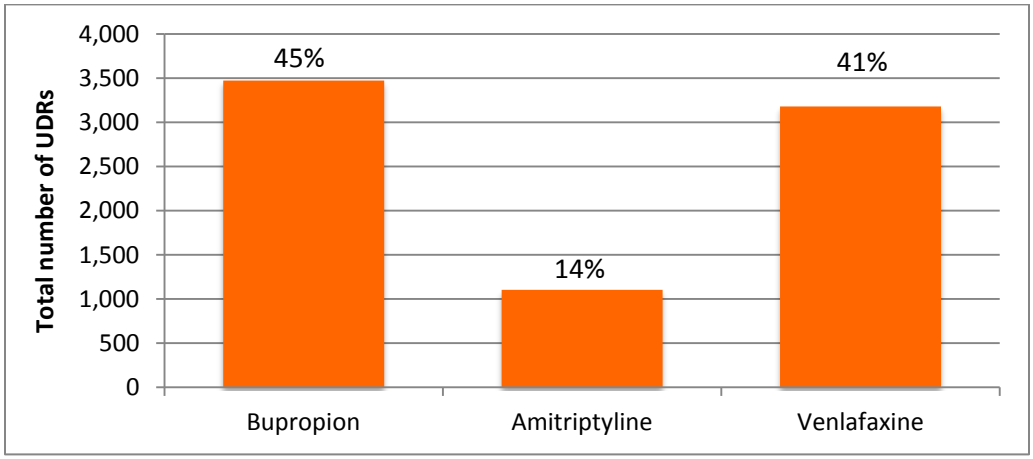
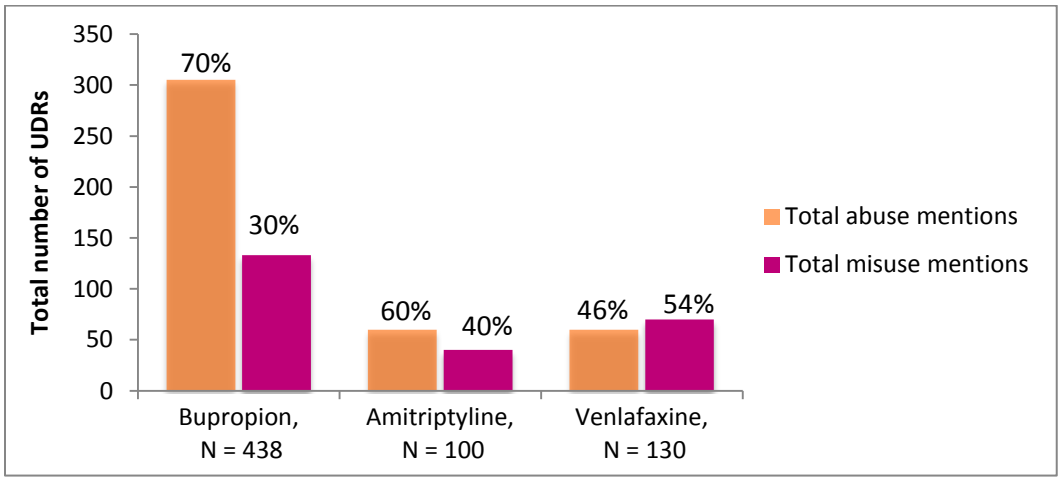


Figure 2: Percentage of total abuse/misuse UDRs by drug (% of *total drug-specific posts*)



- Number of posts of interest (POI), a term coined to denote a post that describes or is related to the abuse or inappropriate use of a drug in question, identified over the study period:
    - Abuse: 425 UDRs (5.4% of 7,756 total UDRs)
        - Bupropion 305, Amitriptyline 60, Venlafaxine 60
    - Misuse*: 243 UDRs (3.1% of 7,756 total UDRs)
        - Bupropion 133, Amitriptyline 40, Venlafaxine 70
    - Discussing/experiencing withdrawal from in-scope drug, 551 UDRs (7.1% of 7,756 total UDRs)
        - Bupropion 67, Amitriptyline 30, Venlafaxine 454[†]

- Discussing/using in-scope drug to attenuate withdrawal of another drug, 209 UDRs (2.7% of 7,756 total UDRs)
    - Bupropion 125, Amitriptyline 31, Venlafaxine 53

- Discussing/utilizing in-scope drug to 'come down' from a high, 11 UDRs (<1% of 7,756 total UDRs)
    - Bupropion 6, Amitriptyline 5, Venlafaxine 0

- Avoiding/discussing drug interactions with in-scope drug, 1,497 UDRs (19.3% of 7,756 total UDRs)
    - Bupropion 690, Amitriptyline 173, Venlafaxine 634

*If a post contained both an abuse and misuse UDR, it was captured as abuse.

† Venlafaxine has labelled known 'withdrawal syndrome' that is described in the label, which may explain the high number of posts in this withdrawal category.

- Number of total posts needed to identify a POI:
    - For abuse/misuse only: 668 UDRs in 7,756 total reviewed = 1 UDR per 12 UDRs
    - For all POI as above: 668 abuse/misuse + 551 withdrawal + 209 attenuating withdrawal + 11 'come down' from high + 1,497 interactions = 2,936 total POI UDRs in 7,756 total reviewed = 1 UDR per 3 UDRs
- To better contextualize the overall numbers of these posts, the numbers of posts for drugs of known high abuse potential were also requested and are available for comparison in Table 18.

Table 18: Total numbers* of posts for seven different drugs

Product	Bluelight	Opiophile	TOTAL
Bupropion	4,058	39	4,097
Amitriptyline	1,183	6	1,189
Venlafaxine	3,508	19	3,527
Methylphenidate	12,274	95	12,369
Alprazolam	41,334	835	42,169
Buprenorphine	44,639	1,538	46,177
Oxycodone	104,270	2,269	106,539

* Total numbers before any deduplication or manual review of posts; thus different from the final product numbers for in-scope products presented above for the most appropriate comparisons to be made.

- Calculation of bupropion exposure and abuse rates from IMS sales data
    - The cumulative postmarketing exposure to bupropion since launch (using IMS data from 1991 to 1997 and GSK sales data since 1998) is approximately 134,161,362 patient exposures up to 31 December 2015.
    - Bupropion total abuse/misuse UDRs per exposure over time thus calculated as 438 mentions per 134,161,362 patient exposures, giving 1 abuse mention in the data source per 306,304 known patient exposures worldwide since 1991. This number is included here as it has been suggested that such data may be used to watch trends over time in FDA draft guidance documents ([FDA], see also section 6.1). Such numbers must be interpreted carefully. It is based on data from only two websites since 1997 at earliest for numerator, while worldwide data for sales since 1991 are used as the denominator (see also section 9.6.1, Limitations).

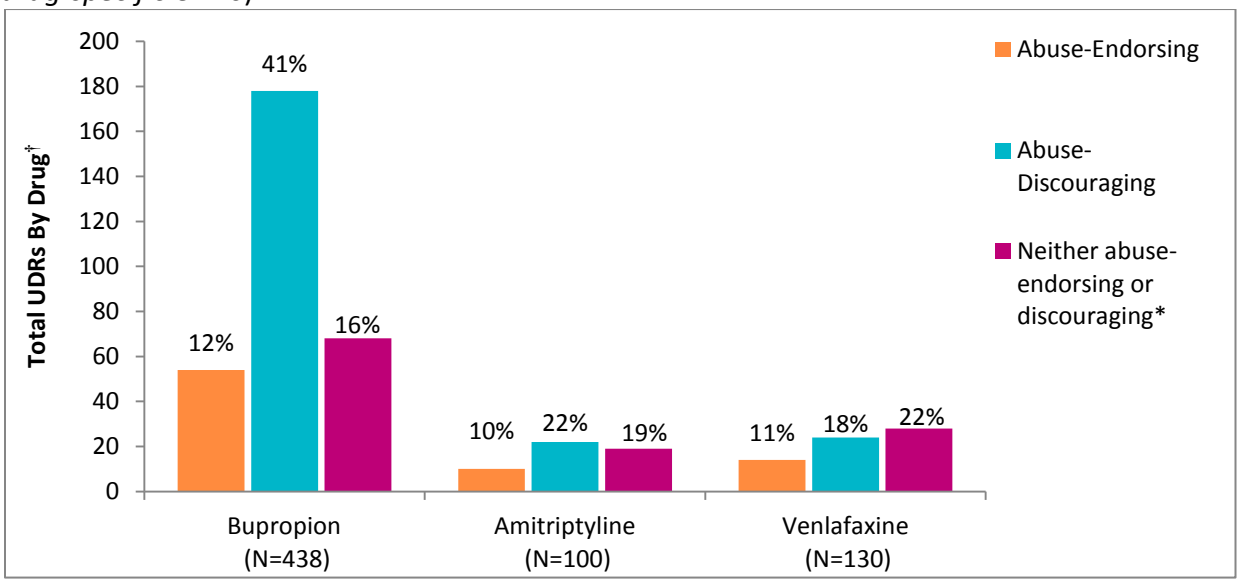
10.5 Main results

10.5.1 Post authors encouraging vs. discouraging use of the drug

Determination of whether a post author was encouraging or discouraging abuse of the drug was available for 417 total posts (62% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 300 of these posts (68% of the 438 total bupropion abuse/misuse UDRs). Distribution of encouraging vs. discouraging or "neither" is detailed in Figure 3 below. Note that percentages do not add up to 100% as the "unknown/not discussed" posts are not included here. A classification of "neither" was assigned if a post was both encouraging and discouraging, as in this example:

"*bupropion is sometimes referred to as crack so I would strongly suggest not mixing the two. This could cause seizure. However, you can have effects from snorting—it burns like h***. People have told me its better than adderal and they have abused it for a long time.*"

Figure 3: Discussions described as abuse-encouraging, discouraging or neither (% of *drug-specific UDRs*)*



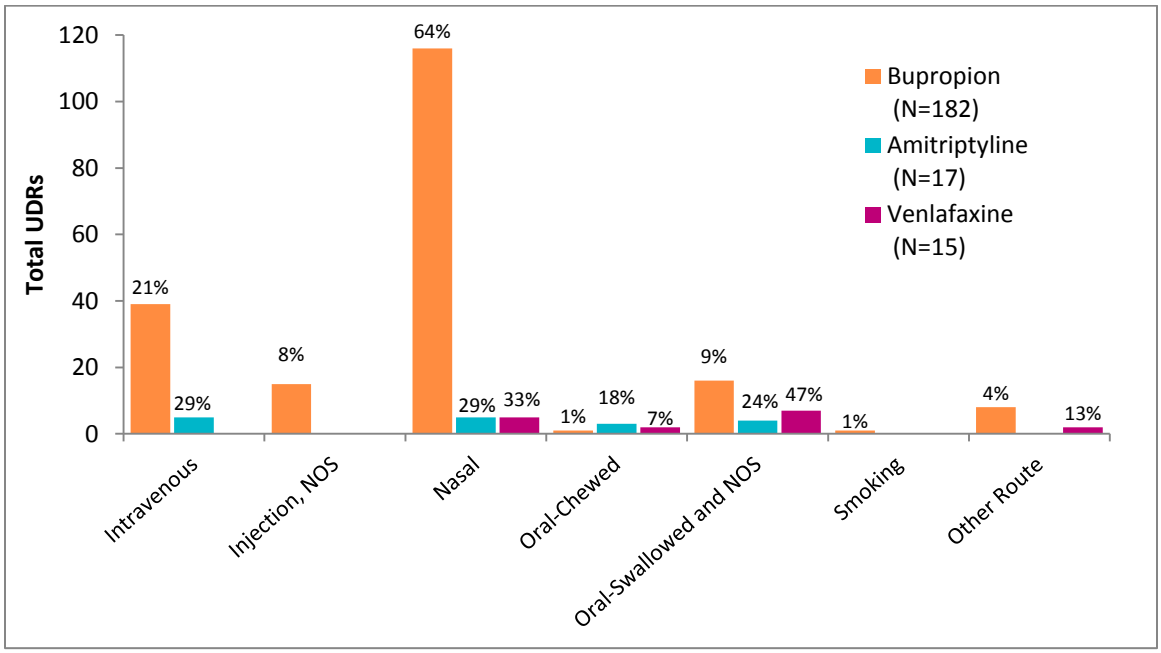
* If a post was both encouraging and discouraging it was captured as 'neither', as in the above example

† Note that percentages do not equal 100%, as unknown/not discussed posts are not included

10.5.2 Route of Administration Details

Route of administration information was available for 214 total posts (32% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 182 of these posts (42% of the 438 total bupropion abuse/misuse UDRs). Distribution of the routes is detailed in Figure 4 below. Note that some percentages may add up to more than 100% due to more than one route being referenced in 21 bupropion posts. "Other" routes of administration noted included plugging/rectal, parachuting (a method of swallowing **drugs** by rolling or folding powdered or crushed **drugs** in a piece of toilet paper to ingest while avoiding the taste of the chemical, foiling (heating a drug on foil and inhaling its vapours), and "abusing any other way".

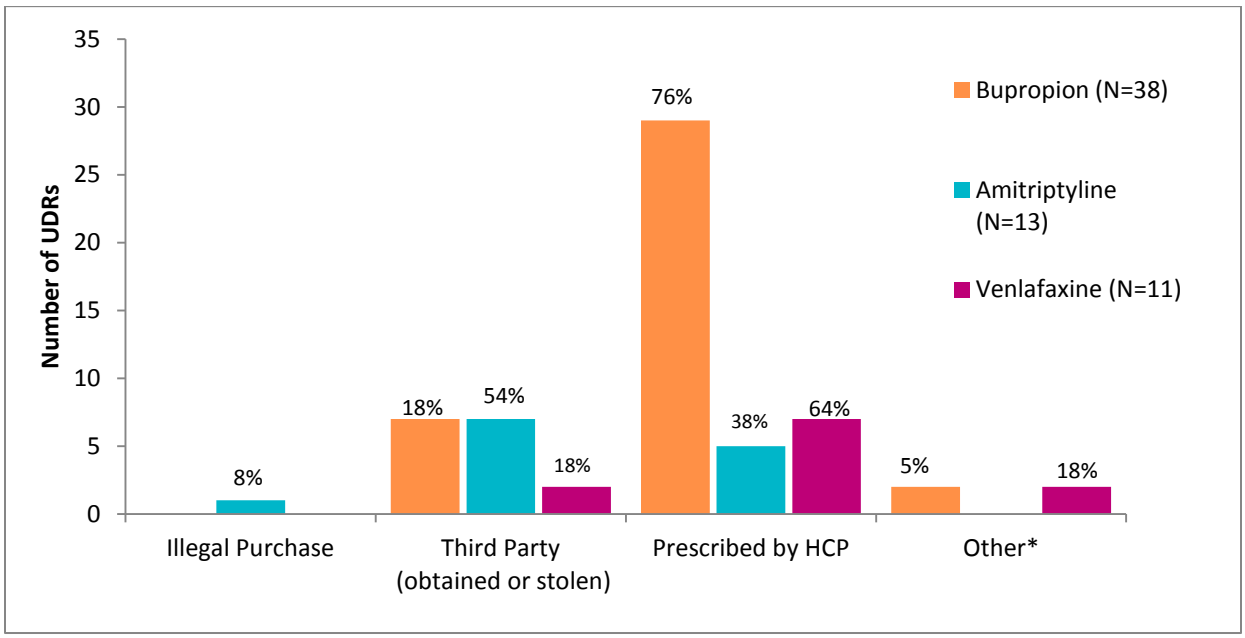
Figure 4: Route of administration details by drug (% of *drug-specific UDRs*)



10.5.3 Information about how drug was procured for abuse/misuse

Method of drug procurement information was available in 62 posts (9% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 38 of these posts (9% of the 438 total bupropion abuse/misuse UDRs). Distribution of the procurement methods is detailed in Figure 5 below. "Other" methods of procurement noted included "came across", "found on ground", "by accident"/ implied pharmacy dispensing error.

Figure 5: Method of procurement details by drug (% of *drug-specific UDRs*)



10.5.4 Desired effect of drug abuse/misuse details

10.5.4.1 Desired effects

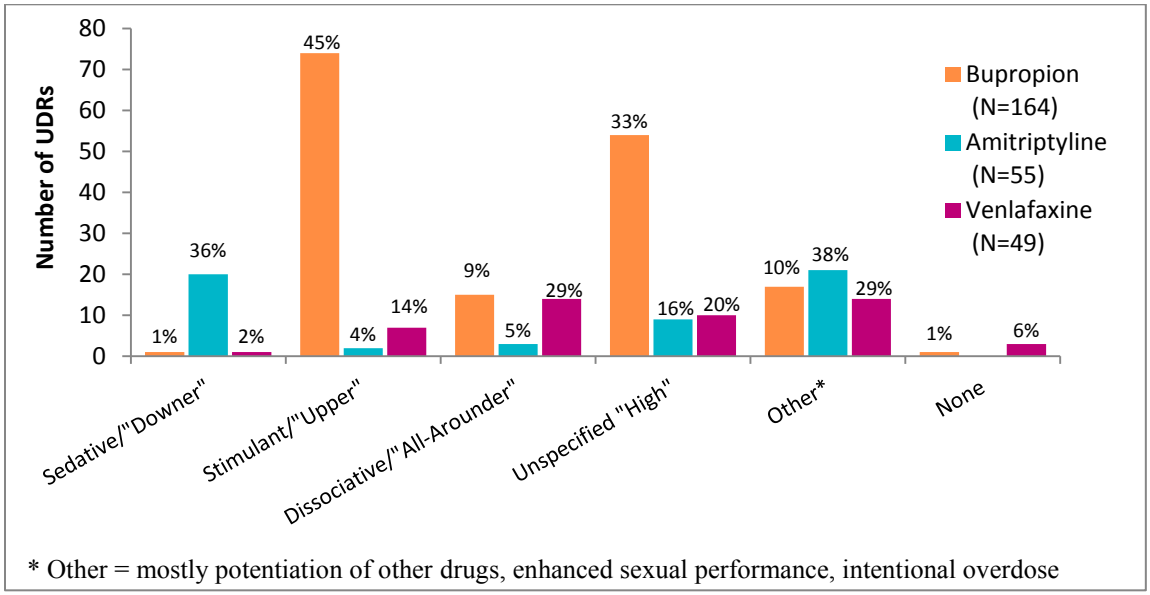
Apparent desired effect of the drug being abused or misused was available in 266 posts (40% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 162 of these posts (37% of the 438 total bupropion abuse/misuse UDRs). Distribution of the procurement methods is detailed in Figure 6 below. As noted in Section 9.8.1.4, desired effect was captured regardless of whether it was apparent that the desired effect was actually achieved.

Categories used by curators for desired effect were as noted in section 9.4:

- Stimulant-like ("upper")
- CNS sedative-like ("downer")
- Other dissociative effects and hallucination ("all arounder")
- Unspecified high—post author refers to a "high" with no further information to determine placement in to one of the above categories
- Other—"Other" desired effects included mostly potentiation of other drugs, enhanced sexual pleasure, and intentional overdose. This category was used at the discretion of the curator if the effect described in the post did not fit into one of the above categories.
- None—this category was chosen in rare circumstances when it appeared that the desired effect was not an altered mental state, such as the following example:

  "*It was problematic at first, but my outcomes were so good that I decided to experiment and find a safe, effective (functionality, NOT a "high") regimen.*"

Figure 6: Desired effect information details by drug (% *drug-specific* UDRs)



* Other = mostly potentiation of other drugs, enhanced sexual performance, intentional overdose

10.5.4.2 Desired effects compared specifically to other highs

Direct comparisons were made between the in-scope drug and another specific drug's desired effect or high in 55 UDRs (8% of the total abuse/misuse UDRs across the three drugs), with bupropion accounting for 42 (76%) of those. Table 19 below details the different comparisons made. There was no overlap in the comparisons amongst the three drugs studied, as shown in the shading of the table.

Table 19: Desired effect compared or similar to specific drugs

Desired effect compared to a specific drug	**Bupropion UDRs (% *desired effect comparisons,* bupropion)**	**Amitriptyline UDRs (% *desired effect comparisons,* amitriptyline)**	**Venlafaxine UDRs (% *desired effect comparisons,* venlafaxine)**	**Total UDRs (% *total desired effect comparison* UDRs)**
Amphetamine	5 (12%)	0	0	5 (9%)
Benzodiazepine	0	2 (100%)	0	2 (4%)
Cocaine	27 (64%)	0	0	27 (49%)
Ecstasy	0	0	5 (46%)	5 (9%)
Opiate or Tramadol	0	0	4 (36%)	4 (7%)
Ritalin	2 (5%)	0	0	2 (4%)
Stimulant	4 (10%)	0	0	4 (7%)
Other	4 (10%, ketamine, caffeine, DXM, Viagra)	0	2 (18%, Benzylpiperazine/ BZP, psychedelic)	6 (11%)
TOTAL	42 (76%)	2 (4%)	11 (20%)	55*

* 53 total posts make up the 55 comparisons, as two posts compared drugs to two different other drugs.

10.5.5 Other effects or outcomes noted

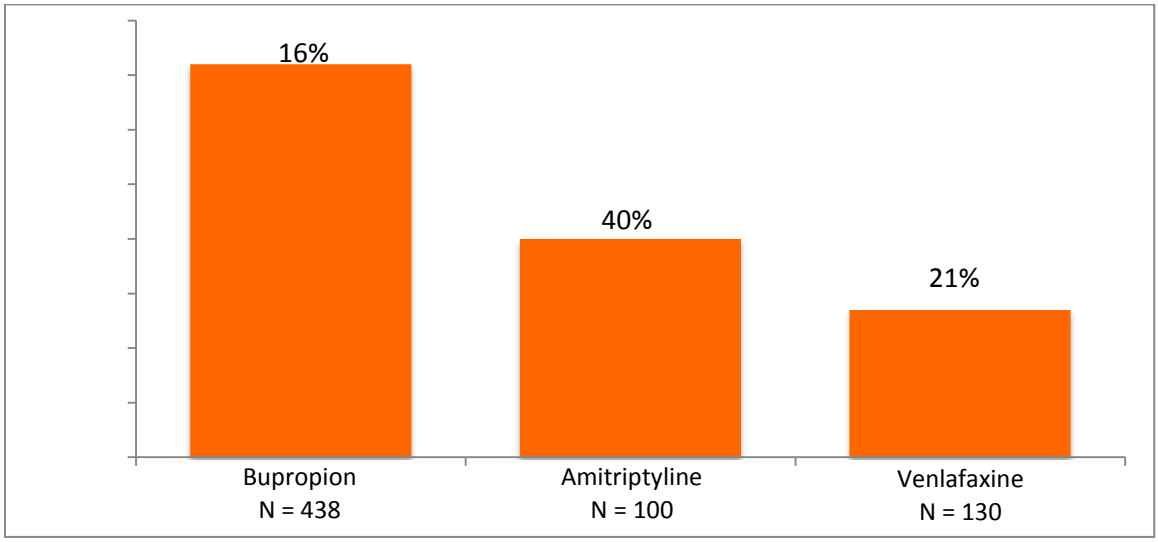
During the curation process, reviewers were also given the chance to state in free-text form any "other outcomes or effects" noted in a UDR. Reviewers were instructed to describe a non-desired outcome or effect of the abuse/misuse (i.e., "seizures with

Wellbutrin" or "ended up in the ER in a coma after amitriptyline use/overuse") whether the outcome was experienced or theoretical/feared. For bupropion, there were 189 abuse/misuse posts that contained such information. In the 189 posts, there were 307 unique events or outcomes noted. These could best be classified mainly as possible adverse events (N = 229, 75%), discussions of positive effects (stimulant, other positive effects, N = 25, 8%), discussions of drug having no recreational value (N = 30, 10%), drug interactions with other substances (N = 19, 6%), Health Systems Interactions (N = 3, 1%), and one report of difficulty tampering with the drug. Of the 229 *experienced or theoretical/feared* adverse events, seizure accounted for 62 (27%), pain with snorting or nasal damage 34 (15%), hallucination 25 (11%), vein or abscess issues 11 (5%), and other negative experiences 12 (5%). Remaining possible adverse events were 5% or less. These were reviewed by the clinical experts on the bupropion safety team, and none were deemed to be unexpected.)

10.5.6 Drug combination for abuse/misuse details

Using drugs in combination for the express purpose of achieving a desired effect in the context of abuse or misuse was referenced in 139 posts (21% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 72 of these posts (16% of the 438 total bupropion abuse/misuse UDRs). Distribution of the combination use across the three drugs is detailed in Figure 7 below. Further details of the specific drugs used in combination with these products were not captured in this study.

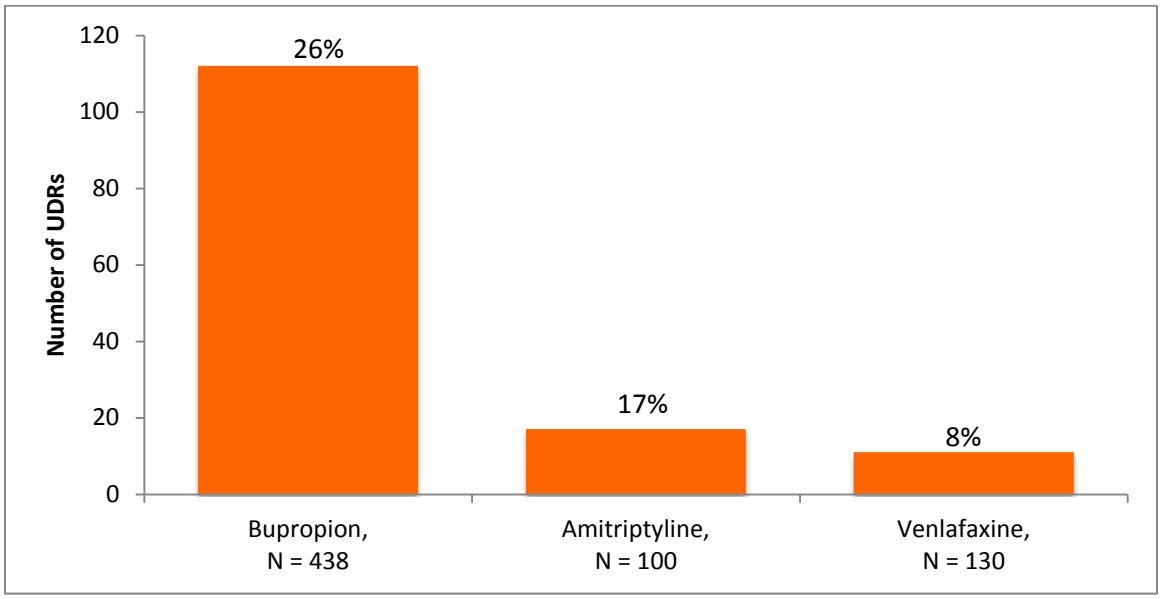
Figure 7: Drugs combined for abuse (% of *drug-specific UDRs*)



10.5.7 Discussion of magnitude of abuse/misuse problem

Magnitude of the abuse/misuse problem, or "community mention" was captured in an attempt to document the prevalence of the abuse problem with the in-scope product. This was marked by curators if a post discussed at least 2 people abusing the same product or specifically negated use by others, or contained any other indication of the size of the abuse problem with the in-scope product. This was noted in 140 posts (21% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 112 of these posts (26% of the 438 total bupropion abuse/misuse UDRs). Distribution of the magnitude of problem UDRs is detailed in Figure 8 below. Of note, manual curators were instructed to assign this category to any post that discussed at least 2 people abusing the same drug or specifically negated use by others, or any other indication of the size of the abuse problem with the in-scope drug.

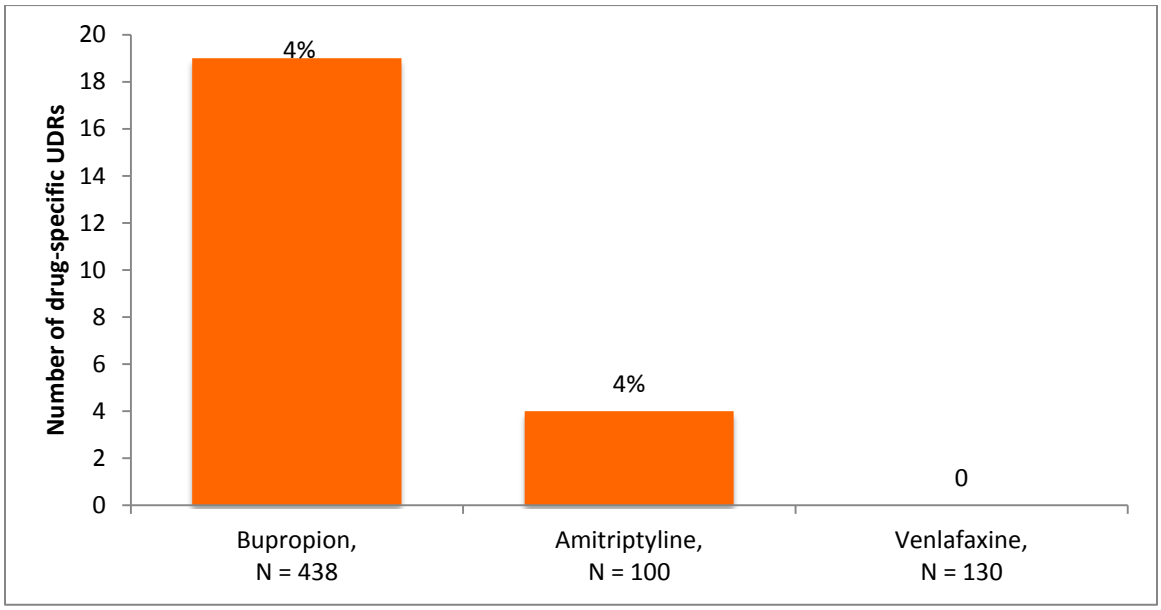
Figure 8: Magnitude of use within the community UDR (% of *drug-specific UDRs*)



10.5.8 Discussion of use within the criminal justice system

Discussion of use within the criminal justice system (use while incarcerated or otherwise in the custody of the criminal justice system) was made in 23 posts (3% of the 668 total abuse/misuse UDRs across the three drugs). This was captured separately in a further attempt to assess the magnitude of bupropion abuse, since the first case reports and series were published from the criminal justice system. Bupropion accounted for 19 of these posts (4% of the 438 total bupropion abuse/misuse UDRs, and 83% of the 23 total UDRs of use within the criminal justice system). Distribution of the criminal justice system UDRs is detailed in Figure 9 below.

Figure 9: Discussions of use within the criminal justice system (% of *drug-specific UDRs*)

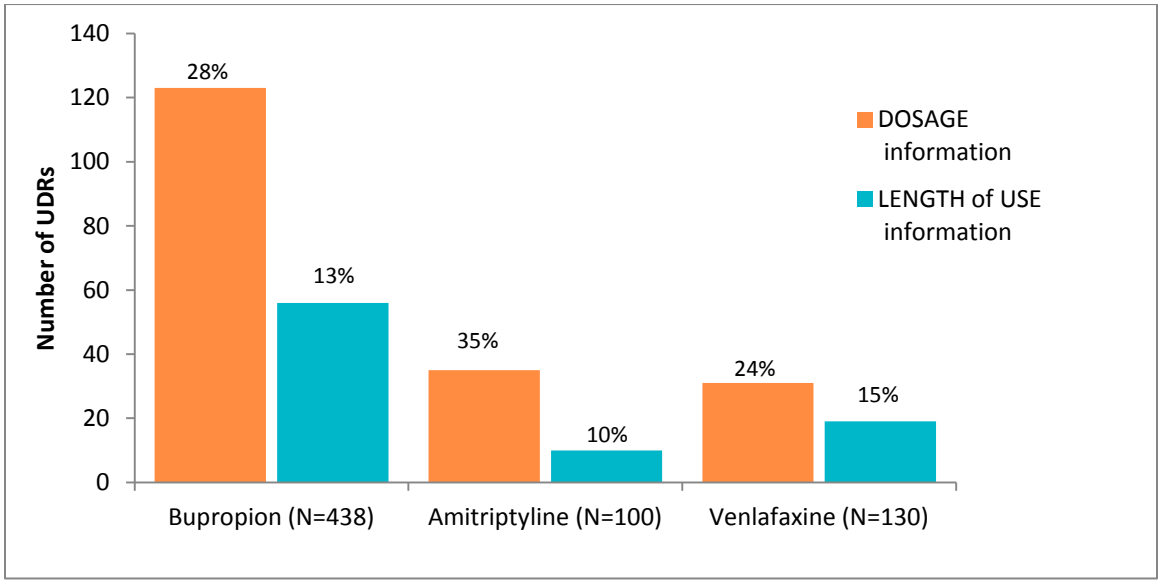


10.5.9 Dosage and length of use information availability and detail

Dosage information was available in 189 posts (28% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 123 of these posts (28% of the 438 total bupropion abuse/misuse UDRs). Length of use information was available in 85 posts (13% of the 668 total abuse/misuse UDRs across the three drugs). Bupropion accounted for 56 of these posts (13% of the 438 total bupropion abuse/misuse UDRs). Distribution of the dosage and length of use availability is detailed in Figure 10 below.

Specific dosages for bupropion ranged from 10 mg to 13,500 mg, with a mean of 731 mg and median of 300 mg.

Figure 10: UDRs with dosage and length of use information (% of *drug-specific UDRs*)



10.5.10 Post authors seeking information about a drug

There were 116 post authors that were seeking specific information about one of the drugs (17% of the 668 total abuse/misuse posts). Bupropion accounted for 67 of these queries (15% of the 438 total bupropion abuse/misuse UDRs). More details about the categories of information sought are provided in Table 20.

Table 20: Seeking information posts (See also Fig A1 in Appendix 1 for graph data)

Type of 'seeking information' posts	**Bupropion posts (% *total bupropion posts seeking information, N = 67*)**	**Amitriptyline posts (*% total amitriptyline posts seeking information, N = 30)***	**Venlafaxine posts (% *total venlafaxine posts seeking information, N = 19)***	**Total seeking information posts (% *total seeking information posts,* N=116)**
General abuse experience	8 (12%)	5 (17%)	4 (21%)	17 (15%)
Abuse experience with routes of administration	22 (33%)	1 (3%)	0	23 (20%)
Misuse experience	5 (7%)	2 (7%)	4 (21%)	11 (9%)
Drug combination abuse experience	15 (22%)	15 (50%)	3 (16%)	33 (28%)
Drug combination abuse experience with routes of administration	2 (3%)	4 (13%)	0	6 (5%)
Drug-drug interactions	12 (18%)	3 (10%)	8 (42%)	23 (20%)
Preparation for abuse	3 (4%)	0	0	3 (3%)

†Drug interaction posts are often describing drug misuse, but are categorized separately here.

10.6 Other analyses: Posts of interest outside of abuse/misuse

10.6.1 Posts of interest defined

In review of the original 7,270 posts containing 7,756 unique drug references, 668 (9%) were tagged per the regulatory-defined criteria for abuse and misuse. We also categorized several other "posts of interest" for the three drugs studied that were also noted during the manual curation of these data. The categories included were as follows, with further definitions included in sections 10.6.2-10.6.5:

- Discussing/experiencing withdrawal from in-scope drug
- Discussing/using in-scope drug to attenuate withdrawal of another drug
- Discussing/utilizing in-scope drug to 'come down' from a high
- Avoiding/discussing drug interactions with in-scope drug

10.6.2 Withdrawal experience post results

These posts were categorized if found to be discussing/experiencing withdrawal from the in-scope drug (even if the drug was being utilized as prescribed). There were a total of 510 posts with 551 drug UDRs, and are further categorized in Table 21.

Table 21: Withdrawal experience post results

	Number of UDRs	% of *total withdrawal UDRs* (N=551)	% *of total in-scope drug UDRs**	% of *total drug UDRs*[†]
Bupropion	67	12%	5%	2%
Amitriptyline	30	5%	9%	3%
Venlafaxine[††]	454	82%	35%	14%

* N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

[†] N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

[††] Venlafaxine has labelled known 'withdrawal syndrome'[3] that is described in the label, which may explain the high number of posts in this withdrawal category.

10.6.3 Use for attenuation of withdrawal from other drug results

These posts were categorized if found to be discussing/using the in-scope drug to attenuate withdrawal of another drug *(this includes references to "help with" coming off or otherwise aiding in the process)* There were a total of 202 posts with 209 drug UDRs, and are further categorized in Table 22.

Table 22: Use for attenuation of withdrawal from other drugs results

	Number of UDRs	% of *total attenuation UDRs* (N=209)	% of *total in-scope drug UDRs**	% of *total drug UDRs†*
Bupropion	125	60%	9%	4%
Amitriptyline	31	15%	9%	3%
Venlafaxine	53	25%	4%	2%

* N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

†N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

10.6.4 Use to "come down" from a high results

These posts were categorized if found to be discussing/using the in-scope drug to help "come down" from a high or other desired effect of another drug. There were a total of 11 posts with 11 drug UDRs, and are further categorized in Table 23.

Table 23: Use to "come down" from a high results

	Number of UDRs	% of *total 'come down' UDRs* (N=11)	% *of total in-scope drug UDRs**	% *of total drug UDRs†*
Bupropion	6	55%	< 1%	< 1%
Amitriptyline	5	45%	2%	< 1%
Venlafaxine	0	N/A	N/A	N/A

* N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

† N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

10.6.5 Discussing/Avoiding Drug Interactions with in-scope drug

These posts were categorized if found to be discussing/avoiding drug interactions with in-scope drug (even if interaction is with a prescribed drug). There were a total of 1,424 posts with 1,497 drug UDRs, and are further categorized in Table 24.

Table 24: Discussing/avoiding drug interactions with in-scope drug*

	Number of UDRs	% of *total interaction UDRs* (N=1,497)	% of *total in-scope drug UDRs*†	% of *total drug UDRs*††
Bupropion	690	46%	52%	20%
Amitriptyline	173	12%	51%	16%
Venlafaxine	634	42%	49%	20%

* Often drug interaction posts were describing misuse as defined by the FDA and utilized for this review. These posts were captured as 'misuse' and not in this section, as in several examples where the author refers to skipping doses of a prescribed drug in order to get high off of another drug.

† N = 1,334 for bupropion, N = 342 for amitriptyline, N = 1,288 for venlafaxine.

††N = 3,472 for bupropion, N = 1,105 for amitriptyline, N = 3,179 for venlafaxine.

10.7 Adverse events/adverse reactions

See section 9.11.3, no reportable adverse events recorded.

10.8 Deviations from original protocol

As noted in sections 7, 9.2, 9.4, and 9.8.2, there were some slight differences in the planned protocol for data analysis and the actual ability to run those analyses after data were received and reviewed. This is likely a function of the novelty of this data source and collection method, making detailed advance planning for analysis difficult in some cases, and does not affect the veracity of any results herein reported.

The differences were as follows:

- Sections 7, 9.8.2: Research question and objectives, Data calculations and transformation after curation—Initial protocol stated that one measured outcome for Objective #1 was "describe 'indicator scores' (a score from 0 to 1 indicating the probability of the post being relevant for topic of interest) for POI vs. non-interest posts". This was not able to be completed in this initial feasibility, given that an initial dataset that has undergone manual review and tagging of these posts is needed in order to begin the training of an automated classifier to assign indicator scores. It is possible that these initial data may be used for that purpose in future research efforts.
- Sections 7, 9.8.2: Research question and objectives, Data calculations and transformation after curation—Initial protocol stated that the two measured outcomes for Objective #2 were "site-specific and population-specific results" of

the study endpoints. Given that only 64 posts (<1%) for the in-scope products came from Opiophile, and the relatively scant amount of demographic information available as reported in Section 10.3 , planned site-specific and population-specific results were not analyzed.

- Section 9.2: Setting—The initial protocol called for evaluation of three websites (bluelight.org, opiophile.org, and erowid.org) It was not possible to obtain permission from Erowid administrators to use their available data for research purposes and the study thus proceeded with only Bluelight and Opiophile data.
- Section 9.2: Setting "Drug abuse, dependence and withdrawal". In the protocol, the PTs for this SMQ were MedDRA v17.1 (18Nov2014). At the time of curation (July 2015), MedDRA version 18.0 was in use. During the change of version, PT *Intentional product use issue* was added to this SMQ. Also of note, it was discovered during the writing of this document that the original protocol duplicated PTs from the "Drug withdrawal" subset of SMQ "Drug abuse, dependence and withdrawal". The protocol also contained PT codes from SMQ "Lack of Efficacy" that were not used as search terms for data gathering.
- Section 9.4: Variables-- During the early review period, curators decided to also add two categories to the classification of "desired effect" of the drug upon noting some ambiguity and difficulty in classifying: Unspecified "high" (when the "high" terminology was used but it was unclear which of the pre-determined categories might be referred to), and "none" (signifying that no psychoactive effect was sought by the abuser/misuse)

11 DISCUSSION

11.1 Key results: where bupropion differed from the comparators amitriptyline and venlafaxine

- Total number of mentions of product reviewed (3,472 [45%] of total UDRs for bupropion, versus 1,105 [14%] for amitriptyline and 3,179 [41%] with venlafaxine)
- Percentage of mentions reviewed containing reference to abuse or misuse of the drug (6% bupropion, versus 1% with amitriptyline and 2% with venlafaxine)
- Post authors' perspective about abuse
    - Abuse-discouraging : bupropion 41% of bupropion abuse/misuse UDRs, amitriptyline 22%, venlafaxine 18%
    - Abuse- encouraging: bupropion 12% of bupropion abuse/misuse UDRs, amitriptyline 10%, venlafaxine 11%
    - Neither encouraging nor discouraging abuse/misuse or neutral/both: bupropion 16% of bupropion abuse/misuse UDRs, amitriptyline 19%, venlafaxine 22%)

- Mention of drugs being combined for abuse, less common for bupropion: (bupropion 16% of bupropion abuse/misuse UDRs, amitriptyline 40%, venlafaxine 21%)
- Mention of the magnitude of abuse or misuse problem within the post author's community (bupropion 26% of bupropion abuse/misuse UDRs, amitriptyline 17%, venlafaxine 8%)
- Route of administration available (bupropion 42% of bupropion abuse/misuse UDRs, amitriptyline 17%, venlafaxine 12%)
- Nasal route of administration (bupropion 64% of known routes of administration for bupropion, amitriptyline 29%, venlafaxine 33%)
- Desired effect of drug noted as stimulant activity or "other" (usually potentiation of other drug effects)
    - stimulant: bupropion 45% of known desired effects for bupropion, amitriptyline 4%, venlafaxine 14%
    - other: bupropion 10% of known desired effects for bupropion, amitriptyline 38%, venlafaxine 29%

11.2 Limitations

11.2.1 General considerations and limitations of evaluating social media may include, but are not limited to, the following:

- Data
    - There is inherent variability across data sources that can change rapidly over time. This may include demographic characteristics of the population posting on a particular website, limitations caused by website characteristics (character limitation), etc.
    - Dynamic online vocabularies may not accurately reflect a given situation. (e.g., a person may say a drug causes their head to "split open" where in reality it gave them a headache).
    - There are numerous reasons why a drug and/or condition may be discussed other than for safety reasons (e.g., discussing a lack of drug sales when earnings are announced, current marketing campaign, etc.).
    - A single individual may post the same information on multiple websites or forums. An attempt is made to remove duplicate posts; however some duplication may still exist after the de-duplication process.
    - The people who post online about experiences with a particular drug may or may not represent the general population or the population who takes the same drug. Therefore, caution should be exercised when generalizing results.

- The frequency of posts with a positive tone or reported experience relative to those with a negative tone or reported experience is unknown; caution should be exercised when comparing the two.
- Data for this evaluation were obtained from publicly available social media channels, with assistance obtained from the site administrators, when applicable

- System
  - Mapping from vernacular to pharmaceutical standard dictionaries is performed through an automated natural language processing algorithm. It is not possible to map all vernacular terms and phrases to structured dictionaries and the mapped terminology may not fully reflect the meaning of the vernacular term. As a result, some meaning may be lost.
  - Quantitative evaluation can be difficult (lack of numerators, denominators, etc).
- Systematic Data Curation
  - Systematic processes, such as noise reduction, may cause the loss of some beneficial data. (See *Data Classification* in Appendix 1)
- Manual Curation
  - The team of curators has undergone standardized training on how to curate posts specific for this project. However, the human element and subjective nature of review allows for the possibility of variance.
- Governance
  - Social listening for post-marketing safety surveillance is a new and developing science. The team's approach may change as regulatory guidance and best practices start to emerge.

11.2.2 Specific limitations for this review

- Protecting PII sometimes necessitates losing context of a post.
- There are multiple definitions of abuse and misuse.[1] Due to the regulatory reporting requirements of this study, the team agreed to use the FDA definitions of both abuse and misuse during the manual curation process.
- The curation of these data is believed to be accurate. Because of the human element involved in manual curation, intra-and inter-rater variability may be present, and accuracy cannot be guaranteed.

11.3 Interpretation

Bupropion is a non-controlled medicine approved in many countries for the treatment of depression and as an aid to smoking cessation. In early preclinical studies, bupropion showed amphetamine-like effects in animals [Bergman, de la Garza, Kamien, Lamb], but human abuse liability studies established that bupropion had lower abuse liability than

amphetamine, methylphenidate and caffeine [Griffith, Miller, Rush, Zernig], leading to non-controlled classification in the United States.

Anecdotal reports of bupropion abuse have emerged [Steele, McCormick, Baribeau, Khurshid, Welsh, Langguth, Hill], with particular focus on criminal justice and prison settings [Del Paggio, Kim, Phillips, Yoon, Hilliard, Reeves]. Given a general paucity of data on nonmedical use of non-controlled substances, this current study was initiated to explore if the misuse and nonmedical use of non-controlled substances can be detected by novel social listening resources.

Those who utilize prescription products outside of the approved formulation or other than the way in which they are prescribed in order to achieve positive psychoactive effects are unlikely to report this use to healthcare providers, drug companies or regulatory agencies, even when adverse events are experienced. In addition, traditional pharmacovigilance tools such as spontaneous adverse event reports, medical literature, observational databases and national surveys have inherent time lags for data availability, often lack product specificity, and may not be specifically tailored for data collection on drug abuse [Dasgupta].

Others have proposed using social media data for surveillance on pharmaceutical products generally [Sarker 2015], and drugs of abuse specifically [Chary, Sarker 2016 Yang CC, Yang M], including semantic approaches [Cameron]. Publicly available data from prominent social media sources have been used to gain a deeper understanding of drug abuse patterns, for example liquid cannabis concentrates [Daniulaityte Drug and Alcohol Dep], recipes for extracting active ingredients from abuse deterrent formulations [McNaughton], and broader understanding of drug use patterns (Hanson). In our current analysis, however, the methodology is extended to include *non*-controlled substances that may have some evidence of abuse.

It is difficult to draw strong conclusions from the bupropion-specific data in this analysis given the novelty of this data source, analysis method, and limitations as noted in sections 9.6 and 11.2 above. We feel, however, that it is reasonable at this point to conclude that this method has shown some promise for future utility and contributed to our overall understanding of this data source.

11.4 Generalisability

These results should not be considered generalisable to the general population nor to the population prescribed any of the involved drugs for two specific reasons:

1. The results are taken from two websites that focus on discussion of misuse and abuse of drugs. As such the posts on these sites may originate primarily from individuals with an interest in misuse and abuse of drugs whose aim is to provide information for others with a similar interest.

2. Lack of demographic information (see section 10.3) makes it impossible to compare this population to any others.

12 OTHER INFORMATION

This novel method for collection of data concerning abuse and misuse of non-controlled substances has not been evaluated, to our knowledge, by any other scientists or groups.

13 CONCLUSIONS

Drug abuse/misuse has been difficult to capture using traditional sources of pharmacovigilance information. The objectives of this feasibility study were to assess the utility of screening social media content as a source of supplementary pharmacovigilance information on drug abuse/misuse. The study, which screened information from two online discussion forums dedicated to recreational drug use and harm reduction, detected some entries related to bupropion, including detailed text descriptions of abuse/misuse experiences. The conclusion from the feasibility study was that these data may be a useful source of information in the future. It was outside the scope of this feasibility study to draw conclusions about the prevalence or health consequences of abuse/ misuse of bupropion from mentions of abuse/misuse on these two online discussion forums.

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Appendix 1. Tables and Figures

Table A1: Breakdown of UDRs within posts over three drugs*

	Bupropion (% of *total* UDRs across all products)	**Amitriptyline (% of *total* UDRs across all products)**	**Venlafaxine (% of *total* UDRs across all products)**	**Total UDRs across all products**
Drug UDRs reviewed	3,472 (45%)	1,105 (14%)	3,179 (41%)	7,756
Abuse/ misuse-related UDRs	438 (6%)	100 (1%)	130 (2%)	668 (9%)

*A single post may contain more than one UDR.

Table A2: Breakdown of abuse vs. misuse UDRs over three drugs

	Bupropion (% of *bupropion abuse/misuse* UDRs)	**Amitriptyline (% of *amitriptyline abuse/misuse* UDRs)**	**Venlafaxine (% of *venlafaxine abuse/misuse* UDRs)**	**Total (% of *total abuse/misuse UDRs,* N = 668)**
Abuse UDRs*	305 (70%)	60 (60%)	60 (46%)	425 (64%)
Misuse UDRs*	133 (30%)	40 (40%)	70 (54%)	243 (36%)
TOTAL (% total *drug- specific* posts)	438 (13% of total bupropion UDRs, N = 3,472)	100 (9% of total amitriptyline UDRs, N = 1,105)	130 (4% of total venlafaxine UDRs, N = 3,179)	668 (9% of total UDRs, N = 7,756)

*If a post contained both an abuse and misuse UDR, it was captured as abuse.

Table A3: Posts encouraging vs discouraging drug abuse

	Bupropion UDRs (% of *bupropion UDRs*, N=438)	**Amitriptyline UDRs** (% of *amitriptyline UDRs*, N=100)	**Venlafaxine UDRs** (% of *venlafaxine UDRs*, N=130)	**Total UDRs** (% of *total abuse/misuse UDRs*, N=668)
Abuse-encouraging	54 (12%)	10 (10%)	14 (11%)	78 (12%)
Abuse-discouraging	178 (41%)	22 (22%)	24 (18%)	224 (34%)
Neither abuse-discouraging or encouraging	68 (16%)	19 (19%)	28 (22%)	115 (17%)
Total	300 (68%)	51 (51%)	66 (51%)	417 (62%)

Table A4: Route of administration information details*

	Bupropion UDRs (% *total routes known for bupropion*, N = 182)	**Amitriptyline UDRs** (% *total routes known for amitriptyline*, N = 17)	**Venlafaxine UDRs** (%*total routes known for venlafaxine*, N = 15)	**Total UDRs** (% *total UDRs where route known**, N = 214)
Route of administration known— Total	182 (42%)	17 (17%)	15 (12%)	214
Intravenous	39 (21%)	5 (29%)	0	44 (24%)
Injection, NOS	15 (8%)	0	0	15 (8%)
Nasal	116 (64%)	5 (29%)	5 (33%)	126 (69%)
Oral- Chewed	1 (1%)	3 (18%)	1 (7%)	5 (2%)
Oral- Swallowed and NOS	16 (9%)	4 (24%)	7 (47%)	27 (14%)
Smoking	1 (1%)	0	0	1 (0%)
Other route (plugging, rectal, parachuting, foiling, "abusing any other way")	8(4%)	0	2 (13%)	10 (5%)

* Some percentages may equal > 100 due to more than one route being discussed in 21 bupropion posts.

Table A5: Procurement information details

	Bupropion procurement method UDRs (% total bupropion *procurement UDRs*)	**Amitriptyline procurement method UDRs (% total amitriptyline *procurement UDRs*)**	**Venlafaxine procurement method UDRs (% total venlafaxine *procurement UDRs*)**	**Total procurement method UDRs (% total *procurement UDRs*)**
Procurement method known— Total	38 (9% of *bupropion total UDRs*, N=438)	13 (13% of *amitriptyline total UDRs*, N=100)	11 (8% of *venlafaxine total UDRs*, N=130)	62 (9% of *total drug UDRs*, N=668)
Illegal purchase	0	1 (8%)	0	1 (0%)
Obtained or stolen from a third party	7 (18%)	7 (54%)	2 (18%)	16 (27%)
Prescribed	29 (76%)	5 (38%)	7 (64%)	41 (66%)
Other ("came across", "found on ground", "by accident"/ implied pharmacy dispensing error)	2 (5%)	0	2 (18%)	4 (6%)

Table A6: Desired effect information details

	Bupropion desired effect UDRs (% *desired effect known* bupropion)	**Amitriptyline desired effect UDRs (% *desired effect known* amitriptyline)**	**Venlafaxine desired effect UDRs (% *desired effect known* venlafaxine)**	**Total desired effect UDRs (% total *desired effect known*)**
Desired effect apparent (sedative, stimulant, other dissociative effects, unspecified "high")- Total	162 (37% of *all bupropion* UDRs, N=438)	55 (55% of *all amitriptyline* UDRs, N=100)	49 (38% of *all venlafaxine* UDRs, N=130)	266 (40% of *all drug* UDRs, N=668)
Sedative ("downer")	1 (1%)	20 (36%)	1 (2%)	22 (8%)
Stimulant ("upper")	74 (45%)	2 (4%)	7 (14%)	83 (31%)
Other Dissociative/All-arounder	15 (9%)	3 (5%)	14 (29%)	32 (12%)
Unspecified High	54 (33%)	9 (16%)	10 (20%)	73 (27%)
Other	17 (10%)	21 (38%)	14 (29%)	52 (20%)
None	1 (1%)	0	3 (6%)	4 (2%)

Table A7: Drugs combined for abuse

	Bupropion drugs combined UDRs (% of *total bupropion UDRs*, N=438)	**Amitriptyline drugs combined UDRs (% of *total amitriptyline UDRs*, N=100)**	**Venlafaxine drugs combined UDRs (% of *total venlafaxine UDRs*, N=130)**	**Total UDRs (% of *total abuse/misuse UDRs*, N=668)**
Drugs combined for abuse	72 (16%)	40 (40%)	27 (21%)	139 (21%)

Table A8: Discussion of magnitude of abuse/misuse problem within the community

	Bupropion community mention UDRs (% of *total bupropion UDRs*, N=438)	Amitriptyline community mention UDRs (% of *total amitriptyline UDRs*, N=100)	Venlafaxine community mention UDRs (% of *total venlafaxine UDRs*, N=130)	Total UDRs (% of *total abuse/misuse UDRs*, N=668)
Discussion of magnitude of abuse/misuse within community (see Figure 8)	112 (26%)	17 (17%)	11 (8%)	140 (21%)

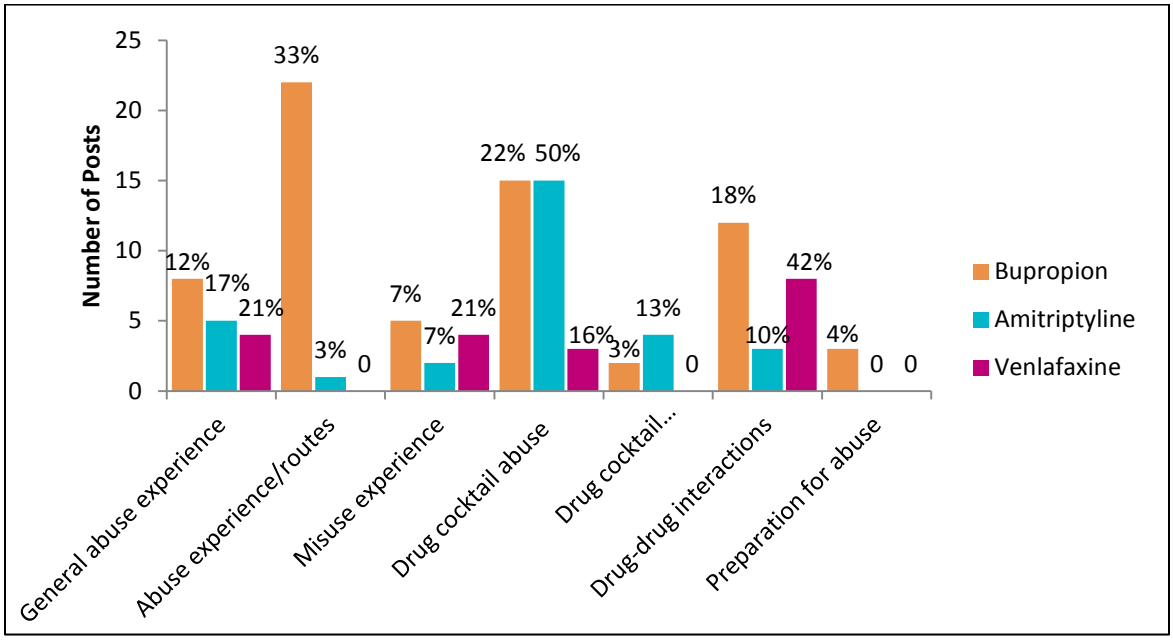
Table A9: Discussion of drug use within the criminal justice system

	Bupropion criminal justice system UDRs (% of *bupropion UDRs*, N=438)	Amitriptyline criminal justice system UDRs (% of *total amitriptyline UDRs*, N=100)	Venlafaxine criminal justice system UDRs (% of *total venlafaxine UDRs*, N=130)	Total UDRs (% of *total abuse/misuse UDRs*, N=668)
Discussion of use within the criminal justice system (see Figure 9)	19 (4%)	4 (4%)	0	23 (3%)

Table A10: Dosage and length of usage information

	Bupropion dosage/length of use UDRs (% of *total bupropion UDRs*, N=438)	Amitriptyline dosage/length of use UDRs (% of *total amitriptyline UDRs*, N=100)	Venlafaxine dosage/length of use UDRs (% of *total venlafaxine UDRs*, N=130)	Total UDRs (% of *total abuse/misuse UDRs*, N=668)
Dosage information known (See Figure 10)	123 (28%)	35 (35%)	31 (24%)	189 (28%)
Length of dosing known (See Figure 10)	56 (13%)	10 (10%)	19 (15%)	85 (13%)

Figure A1: 'Seeking information' posts (% of *total seeking information posts*, N=116)



ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	*None*		

ANNEX 2. ADDITIONAL INFORMATION

FINAL_SIGNED_Protocol_Amendment.pdf

…

Or in the Following Pages:

1. **Original Protocol, full word document version**
2. **Original Protocol signatory page (see page 103)**

TITLE PAGE

Division: Worldwide Development
Retention Category: GRS019
Information Type: Worldwide Epidemiology Study Protocol

Title:	Can social listening data be used to provide meaningful insights into abuse or inappropriate use of bupropion? (A feasibility analysis)

Compound Number:	GR67205
Development Phase	IV
Effective Date:	24 June 2015
Subject:	Drug abuse in relation to drug safety
Author(s):	[redacted]

PASS information

Title	**Can social listening data be used to provide meaningful insights into potential abuse or inappropriate use of bupropion? (A feasibility analysis)**
Protocol version identifier	02
Date of last version of protocol	12/12/14

EU PAS register number	Registered 20 Jan 2015
Active substance	GR67205 [List of pharmacotherapeutic group(s) (ACT codes) and active substance(s) subject to the study]
Medicinal product	Wellbutrin, Wellbutrin XL, Wellbutrin SR, Zyban
Product reference	GR67205
Procedure number	[If applicable, Agency or national procedure number(s), e.g. EMA/X/X/XXX]
Marketing authorisation holder(s)	Glaxo Wellcome UK Stockley Park West Uxbridge Middlesex UB11 1BT
Joint PASS	No
Research question and objectives	**Can social listening data be used to provide meaningful insights into potential abuse or inappropriate use of bupropion?** Objectives: 4. To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities 5. To explore the utility of three internet forums to identify cases of interest 6. To describe and characterize the posts of interest (POI) identified during this feasibility analysis (POI is a term coined to denote a user post that may be relevant to drug abuse or inappropriate use of the product in question)

Country(-ies) of study	Worldwide (internet data from English-speaking sites, from much of which no geographic data will be available)
Author	[redacted] MD, RPh, FACOG [redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Glaxo Wellcome UK Stockley Park West Uxbridge Middlesex UB11 1BT UK
MAH contact person	[redacted] contracting safety physician on behalf of GSK

1. TABLE OF CONTENTS

PAGE

AE	Adverse Event
API	Application Programming Interfaces
CRaWL	Contextualizing ReAl World use of drugs through social Listening, a project sponsored by the Pharmacovigilance Center of Innovation
CSD	Central Safety Department
GSK	GlaxoSmithKline
HCPs	Health Care Professionals
PII	Personally Identifiable Information
POI	"Post of interest", a term coined to denote a user post that may be relevant to drug abuse or inappropriate use of the product in question
RSS Feeds	Rich site summary feeds

2. RESPONSIBLE PARTIES

- [redacted] principle investigator, SERM Manager, CMO GCSP Mature Products US
- [redacted] SERM Director, CMO GCSP SERM US
- [redacted] Contracting Safety Physician, Pharmacovigilance Center of Innovation
- [redacted] SERM Director, CMO GCSP Mature Products US and Pharmacovigilance Center of Innovation
- [redacted] Chief Data Scientist, Epidemico™
- [redacted] Epidemiology Director, Pharma R and D
- [redacted] SERM Manager, CMO GCSP SERM UK
- [redacted] SERM Medical Director, CMO GCSP SERM UK
- [redacted] Medical Advisor, NS, Classic and Established Medicines
- [redacted] US Medical Affairs

SPONSOR SIGNATORY:

[redacted] MD, RPh, FACOG Primary Author of Protocol/ Project officer	**Date**
[redacted] Head, UK SERM Development Therapy Area Leader	**Date**

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: eTrack Study Number 202115

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address

GlaxoSmithKline Research & Development Limited
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: [redacted]

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor Contact Information: n/a (noninterventional)

3. ABSTRACT

Title:

Rationale and background:

Purpose: to determine the feasibility of using social media for collecting meaningful insights into potential abuse or inappropriate use of bupropion.

Rationale: From proof of concept evaluations for Project CRaWL (Contextualizing Real World drug use through social Listening), we know that information about abuse or inappropriate use potential of marketed GSK drugs is available through social listening (the process of identifying and assessing what is being said about a company, individual, product or brand on the Internet). The quality and quantity of those data are not fully explored at this time or in any formal evaluation setting.

These data are typically quite scant in the standard tools used for pharmacovigilance (spontaneous adverse event reporting, observational databases, and literature reports) as abusers are unlikely to report adverse events or means of abuse to regulatory authorities or often even their personal physician. In a recent review of data from the DAWN database, it was reported that, "There are several limitations to the data used in the study, which preclude the ability to make strong recommendations as to the abuse potential of bupropion." [Bibeau,2012] (The data, however, did not provide evidence that abuse of bupropion was growing,)

Knowing that there are some data available from online forums and even mainstream social media sites, we believe that further exploration of these data may be useful. In this feasibility study for bupropion as an example drug, we hope to describe the best use of the data collection tool that we are using through a partnership with Epidemico™, an informatics company with interest and experience in this realm.

Background

Bupropion hydrochloride was first approved in the US in December of 1985 and is currently approved in 80 countries, for depression, smoking cessation, and for seasonal affective disorder. It is classified as a substance of low abuse potential [Miller, 1983; Griffity, 1990; Rush, 1998; Zernig, 2004].

Abuse of bupropion has been described in published case reports, and was first recognized in the setting of correctional institutions where illicit drugs are less available and where bupropion may be widely ordered as a smoking cessation therapy for prison inmates. Most of these reports involve routes other than oral use (the only approved route of administration) including nasal insufflations and intravenous injection [Kim, 2010; Barribeau, 2013; Hilliard, 2013; Reeves, 2013; Yoon, 2013]. During a recent search of the DAWN database there was a paucity of data on route of administration or confirmation of psychoactive effects [Bibeau, 2012]. This is one potential area where social listening data may help significantly augment the existing sources of information that we have on bupropion's abuse or inappropriate use potential.

Research question and Objectives:

- To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities
- To explore the utility of three internet forums to identify cases of interest
- To describe and characterize the posts of interest (POI) identified during this feasibility analysis

Study Design:

This is a retrospective descriptive observational study, analyzing all available data collected on bupropion and comparator drugs (venlafaxine and amitriptyline, as noted in section 7) from three internet forums known to be rich with drug abuse data. Summary statistics on numbers of posts, threads, and authors for drugs of known high abuse potential will also be collected and provided for contextualization of the bupropion and comparator data.

Population:

Data, from publically available social media or internet forum posts from individuals who choose to post on a number of sites will be collected by Epidemico[tm] through the DataSift[TM] platform or directly from the in-scope website administrators. The population will thus be self-selecting and voluntary, and may include users from any country or background as long as they post in the English language and agree to the site's policies.

Variables: The data recorded will include:

- Number of posts of interest (POI), a term coined to denote a post that describes or is related to the abuse or inappropriate use of a drug in question, identified over the study period
- Demographic data where available: age, gender, geographic location, education level/occupation, race/ethnicity
- Number of total posts needed to identify a POI
- Indicator scores for POI vs posts of non-interest
- Site-specific and population-specific results of above endpoints
- IMS sales data for North America and Europe

Data sources:

All data are to be provided to GSK by Epidemico after application of Epidemico's automated classifying software (see section 9 for further description). Only publically available internet data with NO PII (personal identifying information) will be provided to GSK. Websites to be searched will include bluelight.org, erowid.org, and opiophile.org.

Study size:

All available posts from the above sites will be included. The number of unique patients or posts collected is unknown prior to actual data collection.

Data analysis:

The data obtained will be manually reviewed by GSK's Safety Listening Lab team members with both clinical expertise and experience with the manual curation process for pertinence to drug abuse or inappropriate use of bupropion and comparators. Specific endpoints of interest will include route of administration, dosage and length of use, categorization of euphoric effect, whether prison/criminal justice system is involved, procurement of the drug, magnitude of abuse problem within a community, and combination with other agents (polypharmacy). Outputs will then be graphically displayed and comment will be made on the feasibility of this data collection and reporting method as a tool to enhance current pharmacovigilance efforts. Additionally, inclusion of some exemplary verbatim posts in the final report will help the audience conceptualize the tool and dataset.

Milestones:

Key data collection timelines (timepoints) are as follows:

Day One (TBD after SRT and PRF approval)—Retrospective data received from Epidemico

Day 30— Randomly selected 200 posts reviewed, team meets to discuss initial findings or need for further protocol amendment

Day 120—iterative results reviewed by team and next steps discussed

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	31 Mar 2015	4, 6, 7, 9	• Prospective data collection changed to retrospective • In-scope websites changed and thus wording of objective # 2 changed • Project CRaWL team name changed to Safety Listening Lab • Comparator drug handling changed • No longer focusing only on possible Proto-AEs, but curating all posts • Variable for collection added: Mention of magnitude of the abuse problem within the community	• Learned from direct contact with sites that retrospective data are available and would lead to quicker results • Initial data from planned websites offered no new insights • Project CRaWL concluded, led to creation of Safety Listening Lab March 2015 • Increasing experience with resources needed for manual curation led team to feel more strongly about focusing on unanswered questions and not re-visiting abuse potential of drugs of known high potential • Very little data on performance of the automated classifier in this realm led to team concerns about missing valuable information by relying on the classifier tool to filter the data for us • From Section 9.6.1 below After initial data exploration, new data points may need to be added in order to record unforeseen points.
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	Planned date
Start of data collection	30 May 2015
End of data collection	30 July 2015
<Study progress report 1>	30 September 2015
<Study progress report 2>	

<Study progress report n>	
<Interim report 1>	<Date>
<Interim report 2>	<Date>
<Interim report n>	<Date>
Registration in the EU PAS register	20 Jan 2015
Registration in eTrack (#202115)	6 Nov 2014
SRT Approval	14 Nov 2014, amendment 1 = 6 May 2015
PRF Approval	12 Dec 2014, amendment 1=
Final report of study results	30 December 2016

6. RATIONALE AND BACKGROUND

Abuse potential, as defined in FDA's draft guidance document for Assessment of Abuse Potential of Drugs [FDA, 2010], refers to a drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces. These drugs are characterized by their central nervous system (CNS) activity. Examples of the psychoactive effects they produced include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. Drugs with abuse potential often (but not always) produce psychic or physical dependence and may lead to the disorder of *addiction.* The concept of *abuse potential* encompasses all the properties of a drug, including, for example, chemical, pharmacological, and pharmacokinetic characteristics, as well as fads in usage and diversion history.

Specifically, the FDA states in the draft guidance that, "sponsors should search publicly available databases, including the Drug Abuse Warning Network (DAWN), the National Survey on Drug Use and Health (NSDUH), the Treatment Episode Data Set (TEDS), Monitoring the Future (MTF), and *other databases* [emphasis is protocol author's], to characterize and monitor risks associated with the misuses and abuse of a drug and to estimate the extent of use and abuse of a particular drug."

The draft guidance also includes suggestions for collecting information on the type of data that might be collected for a product (eg abuse or inappropriate use events as "numerator" and amount of drug produced in the same time period as "denominator") that could be compared with information on pharmacologically similar drugs. The FDA also suggests that such data could be used to evaluate trends over time.

Background on bupropion abuse [from PRJ2215]:

In early preclinical studies, bupropion showed amphetamine-like effects in animals. Drug discrimination studies in rodents and primates indicate that the subjective experience (stimulus cue) elicited by bupropion is generalized to stimulants such as d-amphetamine, cocaine, and methylphenidate [de la Garza, 1987; Bergman, 1989;Kamien, 1989; Lamb, 1990] .

Despite the evidence for stimulant effects in animals, suggesting a relevant abuse or inappropriate use potential, several clinical studies in humans indicated that oral intake of

bupropion had lower abuse liability than amphetamine, methylphenidate, and even caffeine. Accordingly, it was concluded that bupropion did not exhibit amphetamine-like characteristics in humans, and the drug has been classified as a substance of low abuse potential [Miller, 1983; Griffity, 1990; Rush, 1998; Zernig, 2004].

Abuse potential had been part of the Benefit Risk Management Plan for bupropion up until 2003 and at that point, had no longer been regarded as a potential risk that required additional/further evaluation outside standard pharmacovigilance monitoring. The current European Risk Management Plan also states that standard pharmacovigilance monitoring applies to abuse potential. Routine pharmacovigilance monitoring during 2013 identified an increase in the number of spontaneous reports of bupropion abuse in the GSK worldwide safety database (OCEANS).

The Bupropion Safety Review Team (SRT) agreed that although the numbers of abuse reports were small relative to the total number of reports for bupropion in OCEANS, there was sufficient information to warrant investigation of the potential effect on public health. PRJ2215 was performed to evaluate the route of administration of bupropion resulting in abuse or misuse of the drug in the DAWN database. There were several limitations to the data used in the study, which precluded the ability to make strong recommendations as to the abuse potential of bupropion. However, the data from this study "did not provide evidence that abuse and misuse of bupropion is growing." [Bibeau, 2012]

The SRT is interested in additional sources of data that may help inform the abuse or inappropriate use potential and real-time abuse of bupropion that may be derived from the proposed study. We plan to use social media listening to better understand bupropion abuse potential.

Background on Social Listening and The Safety Listening Lab Currently, post-marketing safety surveillance relies on data from spontaneous adverse event reports, published literature and observational databases (medical records, insurance claims). These data sources have limitations that include: significant under-reporting (some estimate that less than 10% of adverse events are reported), lack of geographically diverse data (most data come from the United States and Europe), and time lag (most data sources lag 9-12 months).

Social listening, a term used to describe the process of monitoring social media data, is widely used in many industries (and governments) and this led GSK's Central Safety Department (CSD) to ask if social listening could be leveraged for pharmacovigilance. Project CRAWL (**C**ontextualizing **R**e**A**l **W**orld drug use through social **L**istening), a pilot to evaluate the benefits and risks of using social listening for post-marketing safety surveillance, was recently launched to evaluate this technology for routine pharmacovigilance. The evaluation comprised a set of research studies on the data that the tool can provide as well as two pilot projects using the data for GSK drug monitoring. Results from Project CRaWL led to the development of the Safety Listening Lab within the Pharmacovigilance Center of Innovation at GSK. The application of this tool to evaluate abuse concerns for medications for which we are actively seeking new data

sources is one of the first projects of the Safety Listening Lab, spelled out in this protocol.

7. RESEARCH QUESTION AND OBJECTIVE(S)

QUESTION: **Can social listening data be used to provide meaningful insights into potential abuse or inappropriate use of bupropion? (A feasibility analysis)**

Purpose

- The purpose of this analysis is to determine the feasibility of using social media for collecting meaningful insights into potential abuse or inappropriate use of bupropion.

Objectives and Endpoints

Objectives	Measured Outcomes
• To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities	• Number of posts of interest (POI)* identified over a period of time • Total number of posts that must be reviewed in order to identify each POI* • Describe indicator scores for POI* vs non-interest posts
• To explore the utility of three internet forums to identify cases of interest	• Site-specific results of above endpoints • Population-specific results of above endpoints
• To describe and characterize the posts of interest (POI) identified during this feasibility analysis	• Descriptive data

*POI (post of interest) is a post that describes or is related to the abuse or inappropriate use of bupropion. This may be better defined at the end of the feasibility portion of the study. Of note, posts will be reviewed manually by reviewers blinded to site/source in order to guard against introduction of bias here.

8. RESEARCH METHODS

8.1. Study Design

This is a non-traditional feasibility study design using a novel data source which we are collaborating with the informatics company Epidemico^{tm} to apply to pharmacovigilance. The design is essentially a retrospective descriptive observational study. Data will be collected retrospectively from internet websites and forums where drug abuse or inappropriate use may be discussed and voluntarily posted on a public site. Data will be collected on chatter concerning bupropion, as well as other drugs that are known to have lower or similar abuse potentials to bupropion (venlafaxine and amitriptyline). Summary

statistics on numbers of posts, threads, and authors concerning drugs of known high abuse potential (oxycodone, buprenorphine, methylphenidate, and alprazolam) will also be reported to help contextualize the data.

8.1. Setting

Setting: Public internet forums where drug abuse is discussed, including bluelight.org, erowid.org, and opiophile.org. Posts in the English language will be included in our search, and we will collect all posts mentioning bupropion products as well as comparator products (venlafaxine, amitriptyline).

Data will be collected using DataSift™, a commercial social media/Big Data collection and delivery service (see below) and/or in direct cooperation with the website owners. Epidemico™ will then provide their commercially available deidentified data to GSK. The medical product data are acquired from publically available online forums that are accessible through proprietary automated content scraping technology, Application Programming Interfaces (APIs) officially published by the sources/sites, and RSS feeds.

After data are acquired, they undergo classification by Epidemico – a filtering process in which an automated Bayesian classifier removes irrelevant items (including duplicates and spam) and further categorizes the language presented in the data. Using the same conceptual process as spam filters for email, the classifier has been trained with a machine learning algorithm to recognize language that may describe an adverse event. The classifier then uses a proprietary vernacular-to-regulatory dictionary to translate symptoms described in colloquial and slang terms into MedDRA terminology (e.g., "skin looks like a lobster" and "I look like a beet" would be classified to erythema).

An indicator score is thus assigned by Epidemico's software developed for this application, ranging from 0 to 1 and indicating the machine-derived likelihood that the post is related to any adverse event. . Manual review of the posts done by GSK's Safety Listening Lab team members with both clinical expertise and experience with the manual curation process will then inform the cut-off level for this score in potential future applications of the product.

About DataSift (from DataSift website) [DataSift, 2014]

DataSift Inc. is the platform that powers the social economy, enabling companies to aggregate, filter and extract insights from the billions of public social conversations on Twitter, leading social networks and millions of other sources. DataSift provides access to both real-time and historical social data to uncover insights and trends that relate to brands, businesses, financial markets, news and public opinion. Key investors include Insight Venture Partners, Scale Venture Partners, Upfront Ventures and IA Ventures. DataSift has offices in San Francisco, New York City and Reading, U.K.

8.2. Variables

All posts mentioning bupropion products as well as comparators (and common misspellings and slang terms) will be acquired:

- All posts on the in-scope internet sites will be reviewed, as the sites are specifically targeted to chatter concerning abuse or inappropriate use
- All posts will be categorized into
  - Abuse-related
  - Proto-AEs (above indicator score thresholds)
  - Otherwise meaningful mention (zero to indicator score thresholds)
  - Unclear/uncodable or spam (negative indicator scores)

Epidemico's automated classifier will also be applied, which is designed to flag posts where product tampering is mentioned (e.g., for purposes of injecting, snorting, etc), or where any misuse, abuse, or diversion is likely. Bupropion classifier posts will then be manually curated by GSK HCPs with the Safety Listening Lab to remove false positives and to request reclassification of mistakes made by the automated classifier. The manually curated bupropion abuse-related posts will then be described in the following settings. Individual POI may be presented in one or more categories described below as appropriate:

- Route of Administration – through manual review. Reviewers will note if the following were mentioned:
  - Nasal insufflations (e.g., snorting)
  - Oral- chew
  - Oral- swallow
  - Smoking
  - Intravenous
  - Injection
  - Subcutaneous
  - Ambiguous and other routes of administration – internet jargon (during initial feasibility project, will determine possibility of further differentiation amongst routes of administration)

- Dosage and length of use

- Categorization of euphoric effect – for all posts identified as abuse-related, the nature of the high will be broadly characterized as being (example terms that would be mapped to the characterizations follow each term):
  - Stimulant-like ("upper")—CNS stimulation, insomnia, energy/energized, increased heart rate, decreased appetite, seizures, increased confidence, excitement, rush, nervousness, anxiety, anger, euphoria
  - CNS depressant-like ("downer")—sedative, anxiolytic, nerve pill, tranquil/tranquilizer, CNS depression, slowed heart rate, slow respiration, sleep/drowsiness, dull senses, diminished pain, slurred speech, coma, hypnotic

        - Other dissociative effects and hallucination (“all arounder”)—psychedelic, distorted perceptions, nausea, dizziness, sweating, raised blood pressure, distorted sensory messages, illusion, altered perception, intensified external stimulus perception, delusions, delirium
        - Unknown or unspecified

    - Prison/criminal justice flag
        - Given the nature of the case reports, any interaction with the criminal justice system (prison, jails), etc. will be manually flagged using a dichotomous indicator.

    - Procurement comments—drug prescribed for patient, obtained/purchased illegally from street/market, obtained/stolen from family member or other acquaintance

    - Polypharmacy: extraction of the names of other substances ingested simultaneously or in combination with bupropion

    - IMS Sales data for North America and Europe

    - Demographic information where available: age, gender, geographic location, education level/occupation, and race/ethnicity

    - Mention of magnitude of the abuse problem within the community

8.2.1. Outcome definitions

- "Drug abuse, dependence and withdrawal" SMQ (see Annex One)
    - Combined category --
        - Abuse
        - Misuse
        - Dependence
        - Overdose
        - Diversion

8.2.2. Exposure definitions

Exposures for capture will include all posts mentioning bupropion or any of the comparator drugs in the English language.

8.2.3. Confounders and effect modifiers

Confounding and effect modification will not be explored in this non-traditional and non-interventional descriptive study.

8.3. Data sources

See also section 9.2, Setting

Several public internet forums where drug abuse is discussed, including bluelight.org, erowid.org, and opiophile.org. Posts in the English language will be included in our search, and we will collect all posts mentioning bupropion products as well as comparator products (venlafaxine, amitriptyline). Summary statistics will be collected for comparators of high abuse potential also as noted in section 9.1

8.4. Study size

There are no a priori specified hypotheses for this study which would drive sample size calculations. All eligible cases will be included, and we will manually curate all cases obtained for bupropion and comparator drugs venlafaxine and amitriptyline.

8.5. Data management

See also Section 9.2, setting.

Data will be collected by Epidemico using DataSift^{tm}, a commercial social media/Big Data collection and delivery service (see below), as well as directly from website owners where applicable/necessary. Epidemico^{tm} will then ensure the data are deidentified and cleared of all personal identifiable information (PII) before performing automated classification and providing to GSK. Epidemico's medical product data are acquired from online forums that are accessible through proprietary automated content scraping technology, Application Programming Interfaces (APIs) officially published by the sources/sites, and RSS feeds.

After data are acquired, they undergo classification by Epidemico as above – a filtering process in which an automated Bayesian classifier removes irrelevant items (including duplicates and spam) and further categorizes the language presented in the data. Using the same conceptual process as spam filters for email, the classifier has been trained with a machine learning algorithm to recognize language that may describe an adverse event. The classifier then uses a proprietary vernacular-to-regulatory dictionary to translate symptoms described in colloquial and slang terms into MedDRAterminology (e.g., “skin looks like a lobster” and “I look like a beet” would be classified to erythema).

An indicator score is thus assigned by Epidemico’s software developed for this, ranging from 0 to 1 and indicating the machine-derived likelihood that the post is related to drug abuse. Manual review of the posts will then inform the cut-off level for this score in

future applications of the product and real-time use for monitoring bupropion abuse internet chatter.

The automated classifier/indicator score is designed to flag posts where product tampering is mentioned (e.g., for purposes of injecting, snorting, etc), or where any misuse, abuse, or diversion is likely. The manual curation process will lead to review of all abuse-related posts to extract further information.

Manual curation will be conducted by GSK Health Care Providers with specific expertise and used to remove false positives and to request reclassification of mistakes made by automated classifier. A custom interface or standard spreadsheet software may be used for this. Findings can then be fed back in to the process to better inform the machine "learning" and improve the tool.

8.5.1. Data handling conventions

See above. No direct patient cases for handling and all data deidentified for PII before becoming available to GSK.

8.5.2. Resourcing needs

We estimate that approximately 1 FTE for 4-6 weeks will be needed for data analysis, interpretation and reporting. Money will also be spent on data acquisition. These expenses will be covered by the budget for the Safety Listening Lab, sponsored by [redacted]

8.5.3. Timings of Assessment during follow-up

First assessment 30 days after full dataset available, as noted in section 4 above. .

8.6. Data analysis

8.6.1. Essential analysis

Objectives
• To determine if social media can identify cases of potential abuse or inappropriate use of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities
• To explore the utility of three internet forums to identify cases of interest
• To describe and characterize the posts of interest (POI) identified during this feasibility analysis

Objective One: (To determine if social media can identify cases of potential abuse of bupropion which can effectively complement existing sources of data currently used for pharmacovigilance activities)

Data on all reports of bupropion related to abuse will be captured and examined. Data from each post will be extracted and descriptive statistics reported in a summary table as available. (See example table one, Annex One).

After initial data exploration, new data points may need to be added in order to record unforeseen points (such as whether the drug was noted to be for primary or additive effect in the case of significant polypharmacy, whether there is a new term for a drug mentioned that we had not known to look for previously, whether vernacular-to-regulatory mapping was appropriate or needs to be adjusted, or other variables)

Bupropion results will be presented alongside the results of comparator drugs in order to provide some context around frequency of mention and relative public health burden. Formal comparisons of abuse potential across drugs are not possible given the limitations of the data (please see Limitations, Section 9.9). In an effort to adjust for availability/circulation of the drugs, the number of abuse mentions per unit sold will be calculated for each product using available IMS sales data.

Summative graphs can then be used for visual data description as seen in Annex One.

Objective Two: (To explore the utility of three internetforums to identify cases of interest) Data will also be described and graphically displayed based on the site or forum from which it was gleaned (which the manual curators will be blinded to prior to data analysis). Since no a priori definitions of site utility exist in this space, only descriptive reports can be provided.

Objective Three: (To describe and characterize the posts of interest (POI) identified during this feasibility analysis)

Qualitative description of the data will then be reported. Inclusion of some exemplary verbatim posts in the final report will help the audience conceptualize the tool and dataset. Word-mapping or other contextualization tools may also be applied to better understand and describe the chatter about bupropion abuse.

8.6.2. Exploratory analysis

- These will be driven by the essential analyses, but if the sample size permits, we will report the data by route of administration, dosage and length of use, categorization of euphoric effect, prison/criminal justice flag, procurement comments, polypharmacy, IMS sales data, demographic information, and mention of magnitude of the abuse problem within the community to help us understand the strengths and weaknesses of this tool.

8.7. Quality control

This is an original design with data collection for a novel purpose via a novel method. There is no prior validation. This is the reason for including the comparator drugs as well as IMS sales data for denominator comparisons, consistent with the FDA's draft guidance document [FDA, 2010].

8.8. Limitations of the research methods

The current study is primarily designed to assess the utility of social media in detecting a signal of abuse potential of a product.

There are currently some major limitations in the use of social media information in terms of quantitative signal evaluation where the abuse potential of one product is compared to the abuse potential of another product. These limitations relate to missing information for the numerator and unclear denominators for any comparisons of abuse frequency.

Regarding the numerator, mention frequency is likely to be driven by access to the medication (if relatively low availability/ circulation of a drug, the potential for diversion or misuse will be lower). Although we intend to provide some context around the number of bupropion mentions versus other drugs by assessing mentions/ unit sold using IMS sales data as a proxy for availability/circulation, there are limitations to this approach. Sales data may not be available for all countries and there may be access controls applied to a product in some which will not be reflected in the sales data.

Mention frequency may also be affected by the type of experience that the abuse/misuse results in. For example, it may be that more dramatic effects/ experiences ("highs" or psychedelic experiences) are mentioned more frequently than effects such as somnolence. If products differ in the type of experience they elicit, comparisons may be biased due to differential potential for missing information in the numerator.

The extent of information missing from those who abuse/misuse a substance and do not post about it cannot be evaluated. Furthermore, the demographic profile of those who post about their substance abuse/misuse compared to the profile of those who abuse-misuse substances but don't post is relatively unknown. Validation studies which compare the demographic profile of those who abuse/misuse and post versus those who abuse/misuse a product and don't post are likely to be difficult to conduct given the difficulty in identifying those who abuse/misuse substances and the legal implications involved. If a product that is more likely to be abused/misused by individuals who don't post about their experience is compared to a product that is more likely to be abused/misused by people who do post, then these comparisons will be biased.

Other limitations of studying this novel tool include: difficulty mapping vernacular terminology to standard regulatory dictionaries, ever-changing and evolving nature of vernacular speech, and confounding by spam and advertisement-type posts as well as the imperfect nature of the deduplication tools for posts.

8.8.1. Study closure/uninterpretability of results

If data volume is not sufficient for analysis after data collection, we will consider termination of this project.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Informed consents not applicable in this collection of data offered willingly to public internet forums by self-selected patients. Data will be collected only from sites that permit it by their user agreements and ethics approval is not required.

9.2. Subject confidentiality

All data in this study are publically-available and deidentified as part of Epidemico's standard commercial product offerings prior to being provided to GSK. The study team is working with patient privacy experts to ensure that this is protected to the best of our ability and will flag any potential concerns back to Epidemico for continuous quality improvement of the data collection and deidentification system.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

During this study, reportable adverse events will not be noted due to the nature of the deidentified data. The following governance has been put in to place:

- For our social media listening project, we will be purchasing de-identified data from a third party vendor that has been stripped of Personally Identifiable Identification. Therefore, in the absence of an identifiable reporter, we will have no individual case reporting requirements. We will instead report any signals either in an expedited manner or as part of routine aggregate reports in keeping with how we currently treat observational data from other sources.
- In order to ensure alignment and acceptance both internally and externally, we have already consulted and communicated this approach with the FDA, MHRA and EMA, GSB, the OCMO Leadership Team, Global Digital Risk Board, the patient privacy office, PV compliance, regulatory compliance, legal, IT, the joint GCSP/GRA leadership team, and others.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

We will aim to disseminate these results in the form of a peer-reviewed journal article at the end of the project. GSK stakeholders will have the opportunity to review the information generated by the study prior to submission for publication, including the

bupropion clinical team, GCSP and Safety Listening Lab team and sponsors, and any other applicable or interested parties.

11.2. Study reporting and publications

Upon protocol approval, protocol summary will be posted to both the EU PAS Register and the GSK Clinical Study Register (VCTR).

Upon completion of the study, results will be posted on the GSK Clinical Study Register, the EU PAS Register, and will be prepared in manuscript form for journal submission.

12. REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Tables

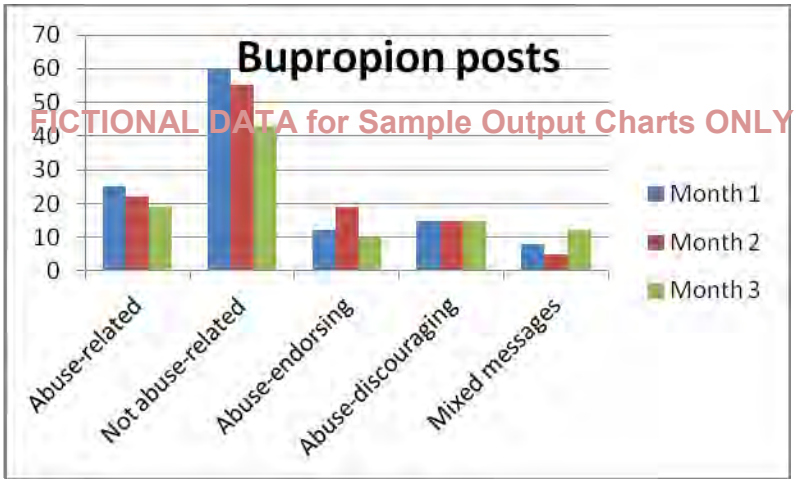
Example table one: Descriptive characteristics of bupropion data

	Bupropion (n)	Bupropion (%)	Venlafaxine controls (n)	Venlafaxine controls (%)	Amitriptyline (n)	Amitriptyline(%)
Number of drug mentions		100%		100%		100%
Number of abuse-related mentions						
Route of Administration: Oral- Chewed						
Oral- swallowed						
Nasal						
Smoking						
Intravenous						
Subcutaneous						
Injection not otherwise classified						
Ambiguous or other						
Categorization of Euphoric Effect: Stimulant-like/"upper"						
CNS-depressant-like/"downer"						
Other dissociative effects or hallucination/"all-						

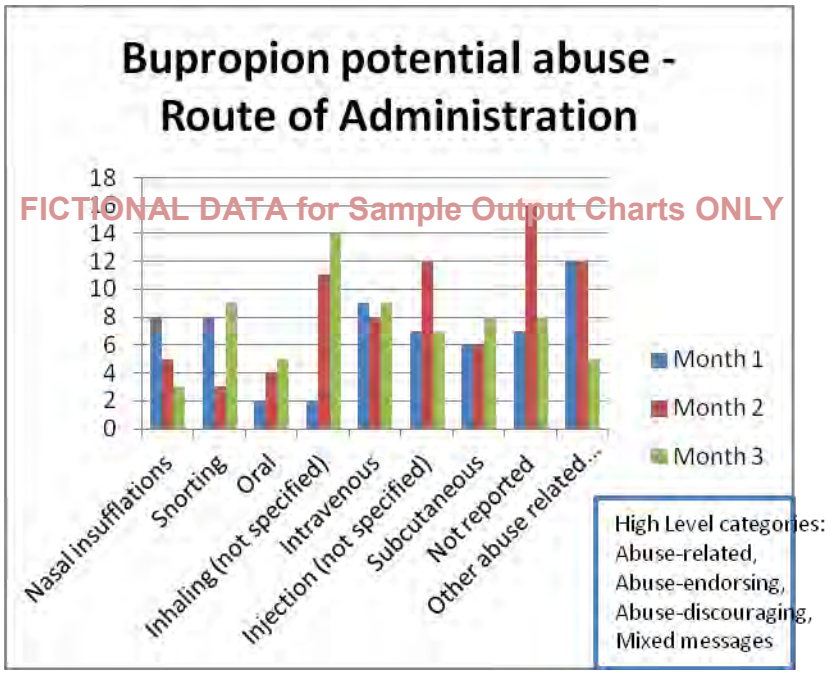
arounder”						
Unknown or unspecified						
Prison or criminal justice involvement?						
Procurement information available?						
Prescribed for patient?						
Obtained illegally (buy/trade)						
Obtained/stolen from family member of acquaintance?						
Polypharmacy/concomitant drugs used?						
Mention of magnitude of abuse problem in community?						

Figures, for example purposes only. Captions will change based on final data availability.

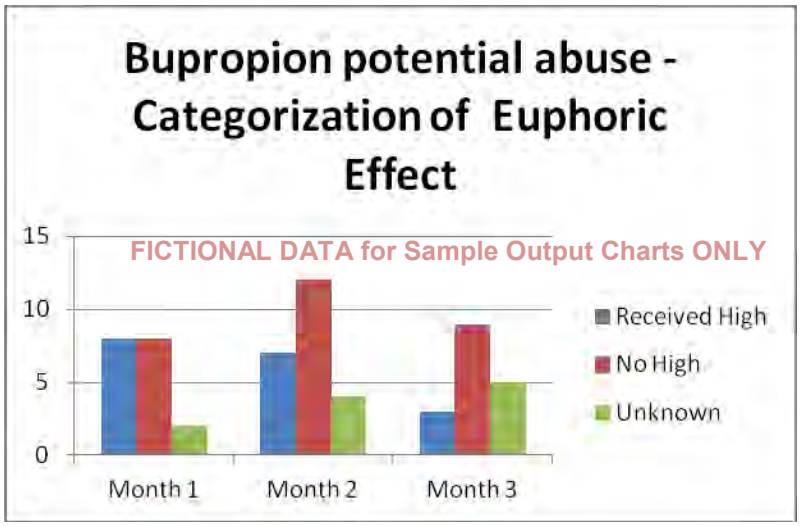
Bupropion – High Level Categories



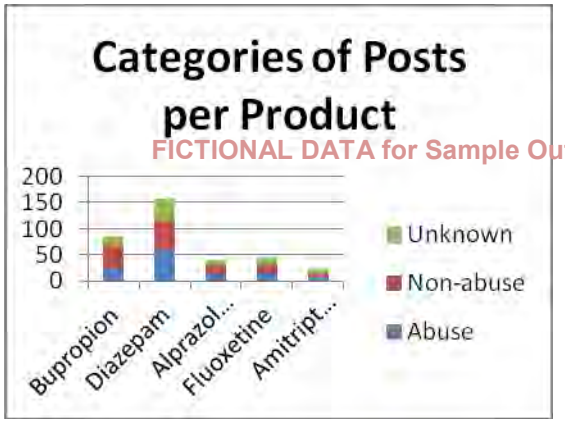
Bupropion potential abuse – Route of Administration

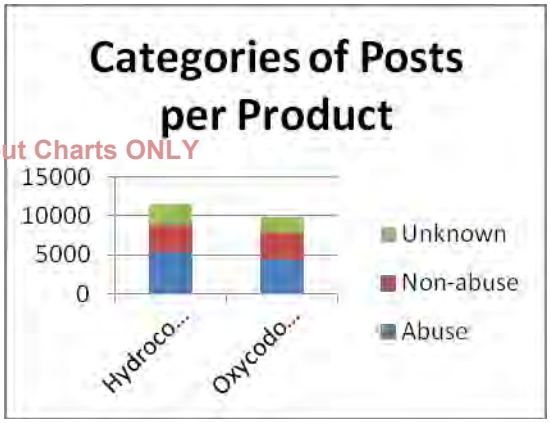


Bupropion potential abuse – Categorization of Euphoric Effect



Categories of Posts per Product





FICTIONAL DATA for Sample Output Charts ONLY

No.	Document Reference No	Date	Title
1.	1	18 Nov 2014	SMQ for drug abuse
2.	<No>	<Date>	<Text>
N	<No>	<Date>	<text>

PT	PT code	SMQ
Dopamine dysregulation syndrome	10067468	Drug abuse and dependence
Drug abuse	10013654	Drug abuse and dependence
Drug abuser	10061111	Drug abuse and dependence
Drug dependence	10013663	Drug abuse and dependence
Drug dependence, antepartum	10013675	Drug abuse and dependence
Drug dependence, postpartum	10013676	Drug abuse and dependence
Intentional drug misuse	10065679	Drug abuse and dependence
Intentional overdose	10022523	Drug abuse and dependence
Maternal use of illicit drugs	10026938	Drug abuse and dependence
Neonatal complications of substance abuse	10061862	Drug abuse and dependence
Polysubstance dependence	10053243	Drug abuse and dependence
Substance abuse	10066169	Drug abuse and dependence
Substance abuser	10067688	Drug abuse and dependence
Accidental overdose	10000381	Drug abuse and dependence
Dependence	10012335	Drug abuse and dependence
Disturbance in social behaviour	10061108	Drug abuse and dependence
Drug detoxification	10052237	Drug abuse and dependence
Drug diversion	10066053	Drug abuse and dependence
Drug level above therapeutic	10061132	Drug abuse and dependence
Drug level increased	10013722	Drug abuse and dependence
Drug screen	10050837	Drug abuse and dependence
Drug screen positive	10049177	Drug abuse and dependence
Drug tolerance	10052804	Drug abuse and dependence
Drug tolerance decreased	10052805	Drug abuse and dependence
Drug tolerance increased	10052806	Drug abuse and dependence
Medication overuse headache	10072720	Drug abuse and dependence
Narcotic bowel syndrome	10072286	Drug abuse and dependence
Needle track marks	10028896	Drug abuse and dependence
Overdose	10033295	Drug abuse and dependence
Prescription form tampering	10067669	Drug abuse and dependence
Substance use	10070964	Drug abuse and dependence
Substance-induced mood disorder	10072387	Drug abuse and dependence
Substance-induced psychotic disorder	10072388	Drug abuse and dependence
Toxicity to various agents	10070863	Drug abuse and dependence
Drug withdrawal convulsions	10013752	Drug withdrawal
Drug withdrawal headache	10013753	Drug withdrawal
Drug withdrawal maintenance therapy	10052970	Drug withdrawal
Drug withdrawal syndrome	10013754	Drug withdrawal
Drug withdrawal syndrome neonatal	10013756	Drug withdrawal
Drug rehabilitation	10064773	Drug withdrawal
Rebound effect	10038001	Drug withdrawal

Steroid withdrawal syndrome	10042028	Drug withdrawal
Withdrawal arrhythmia	10047997	Drug withdrawal
Withdrawal syndrome	10048010	Drug withdrawal
Device defective	10074425	Lack of efficacy/effect
Device failure	10056871	Lack of efficacy/effect
Device ineffective	10059875	Lack of efficacy/effect
Drug effect decreased	10013678	Lack of efficacy/effect
Drug effect delayed	10068303	Lack of efficacy/effect
Drug effect incomplete	10013682	Lack of efficacy/effect
Drug effect variable	10074541	Lack of efficacy/effect
Drug half-life reduced	10049994	Lack of efficacy/effect
Drug ineffective	10013709	Lack of efficacy/effect
Drug ineffective for unapproved indication	10051118	Lack of efficacy/effect
Drug level decreased	10013718	Lack of efficacy/effect
Drug resistance	10059866	Lack of efficacy/effect
Drug specific antibody present	10013745	Lack of efficacy/effect
Drug tolerance	10052804	Lack of efficacy/effect
Drug tolerance increased	10052806	Lack of efficacy/effect
Multiple-drug resistance	10048723	Lack of efficacy/effect
No therapeutic response	10063670	Lack of efficacy/effect
Paradoxical drug reaction	10048958	Lack of efficacy/effect
Tachyphylaxis	10043087	Lack of efficacy/effect
Therapeutic product ineffective	10060769	Lack of efficacy/effect
Therapeutic product ineffective for unapproved indication	10060770	Lack of efficacy/effect
Therapeutic reaction time decreased	10061380	Lack of efficacy/effect
Therapeutic response decreased	10043414	Lack of efficacy/effect
Therapeutic response delayed	10053181	Lack of efficacy/effect
Treatment failure	10066901	Lack of efficacy/effect
Vaccination failure	10046862	Lack of efficacy/effect
Virologic failure	10065648	Lack of efficacy/effect
Drug withdrawal convulsions	10013752	Drug withdrawal
Drug withdrawal headache	10013753	Drug withdrawal
Drug withdrawal maintenance therapy	10052970	Drug withdrawal
Drug withdrawal syndrome	10013754	Drug withdrawal
Drug withdrawal syndrome neonatal	10013756	Drug withdrawal
Drug rehabilitation	10064773	Drug withdrawal
Rebound effect	10038001	Drug withdrawal
Steroid withdrawal syndrome	10042028	Drug withdrawal
Withdrawal arrhythmia	10047997	Drug withdrawal
Withdrawal syndrome	10048010	Drug withdrawal

WWEpi Project number:

SPONSOR SIGNATORY:

[redacted]

MD, RPh, FACOG
Primary [redacted]nor of Protocol/ Project officer

15.6.2015
Date

[redacted]

[redacted] Head, [redacted] Development
Therapy Area Leader

16.6.2015
Date

SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study eTrack 202115.

Name of Project Officer: [redacted]

Title of Project Officer: Contracting Safety Physician, GCSP

Signature: [redacted]

Date: 3 JUNE 2016

Name of Therapy Area Head: [redacted]

Title of Therapy Area Head: VP and Head, SERM Mature Products

Signature: [redacted]

Date: 3rd June 2016

INVESTIGATOR SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge Study eTrack 202115 was carried out as described in this GlaxoSmithKline Report

Name of Investigator: [redacted]

Affiliation: [redacted]

Signature of Investigator: [redacted]

Date: 3 · JUNE · 2016