Original Research Article Pharmacoinformatics

International Journal of Pharma and Bio Sciences

ISSN
0975-6299

ANALYSIS OF ADVERSE REACTION ASSOCIATED WITH DIETARY DRUG ORLISTAT USING DATA MINING ALGORITHMS

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ABSTRACT

Orlistat is a drug given for obesity and treat overweight children and adults. The aim of this work is to analyze the adverse reactions of the drug orlistat from the information available in Adverse Events Reporting System(AERS) using WEKA. The Hoeffding tree algorithm is the best method for inducing decision trees from continuous data streams using Hoeffding bounds and enhanced Hoeffding tree has been developed for analyzing and extracting information from the huge AERS database. The results obtained proved that frequent adverse effects like gastrointestinal disorders, respiratory infections etc were reported at alarming rate.

KEYWORDS: *Orlistat, adverse reactions, Obesity, WEKA, Open vigil.*

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Received on: 06-03-2017
Revised and Accepted on: 26-05-2017
DOI: http://dx.doi.org/10.22376/ijpbs.2017.8.3.p74-80

INTRODUCTION

Overweight and obesity are on a rise throughout the world and its prevalence among teenagers and children are of great concern[1]. The ultimate result of this problem leads to early type 2 diabetes mellitus, hypertension, hyperlipidemia and atherosclerosis, depression and social exclusion. So it becomes very important to control overweight in early age[2]. Prevention is always better than cure and once a person starts suffering from it, change in lifestyle and medication becomes necessary[3].This paper analyses the effect of using orlistat on weight reduction in obese adolescents, and also assesses its safety profile (based on FAERS) and its impact on quality of life of patients.

Literature review

Lot of adverse effects are happening throughout the world due to intake of drugs and concerns about the safety of drugs has given rise to many standard database like Adverse Events Reporting System (FAERS), USFDA for analyzing huge information on adverse effects. Pharmacovigilance is study on the effects of these drugs on population with respect to safety aspect. The effect of some drugs raised concerns with World Health Organization (WHO) creating international committee of drug monitoring, which now has 131 countries with 8 million reports in WHO database. Orlistat, a gastrointestinal lipase inhibitor is a drug available from 1998, meant for reducing dietary fat absorption in obese people. Orlistat intake makes one-third of triglyceride taken in to go undigested[4] and eliminated as stools. When an adult takes Orlistat it decreases weight and BMI when proper dieting and exercise is done[5]. It is an approved drug for obese adults in around 120 countries, with 22 million people having received this drug already[6]. Orlistat was not recommended for obese children as it has no systemic mechanism of action[7].It must be avoided when patient has chronic diarrhea[8].

Table 1
Adverse events related with orlistat and placebo.

Adverse event	Analytical work[9]		Analytical work[10]	
	Orlistat	placebo	Orlistat	placebo
Respiratory infections	20.30%	17.30%	32.40%	26.50%
Flu	39.80%	38.50%	-	-
Hepatitis	-	-	-	-
- = not specified				

From WHO database, based on results given, statistical evaluation was not possible and child obesity problem are discussed[11].

METHODOLOGY

The occurrence of adverse event due to orlistat was analyzed using Open vigil 2 tool. Then the extracted information was analyzed using WEKA 3.8 tool. The total number of adverse events extracted were 46,086 with 2058 different classes of adverse events. A model for the adverse event can be created using Enhanced Hoeffding Tree (EHT) induction algorithm. Hoeffding tree induction algorithm[12] produces decision tree from incoming data stream incrementally. Every sample is analyzed only once and no samples are stored after they are used to update the tree which contains information and grows with time. According to Hoeffding bound, after "*n*" independent observations, with probability $1 - \delta$ the true mean will not vary from estimated mean by a value greater than $\varepsilon = \sqrt{\frac{R^2 \ln(1/\delta)}{2n}}$. Figure 1 shows EHT algorithm that creates a model that learns inline with changing concepts and keeps sufficient statistics for *M.* It uses new samples as validation set to match the model performance created with new and old searches. Old model is pruned when new one is better than old one and search can also be pruned.

EHT(datastr, δ)

Initialize HT as tree having one leaf

Init counts *nijk* at root

for every sample (x, y) in data stream

do increase, decrease and remove samples

EHTGROW((x, y),*HT*, δ)

FINDSPLIT_VALIDITY(*HT*, *n*, δ)

EHTGROW((x, y),*HT*, δ)

quicksort (x, y) leaf *l with HT*

at leaf l update the count

if samples analysed in *l is not of same group*

then find information gain *G* of attribute

if difference of inf. gain of 1st and 2nd best attr.> $\sqrt{\frac{R^2 \ln 1/\delta}{2n}}$

then leaf split on best attribute

for each branch

do create leaf with count

Create another subtree

FINDSPLIT_VALIDITY(*HT*, *n*, δ)

for every node *l* in *HT which* is not leaf

do for each tree T_{alt} in created subtree

do FINDSPLIT_VALIDITY(T_{alt} , *n*, δ)

if new attribute exists in node *l*

do create new subtree

Figure 1
EHT induction algorithm

EXPERIMENTAL RESULTS

The highest occurrence of adverse event due to Orlistat is 2058 with gastrointestinal disorder and occurrence of 20 events was shown in figure 1. The statistical analysis result of chi_square and Proportional Reporting Ratio (PRR) for extracted adverse event for Orlistat in open vigil is shown in figure 2. Figure 3 shows the plot of PRR, Chi_square and Reporting Odd Ratio (ROR) for orlistat associated adverse events. Table 2 provides the top 300 occurance of adverse events out of 2048 classes.

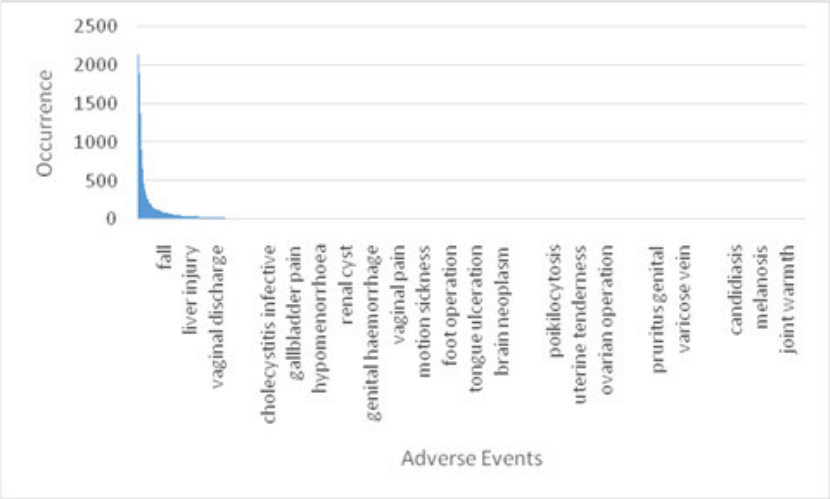

Figure 1
Occurrence of Adverse events

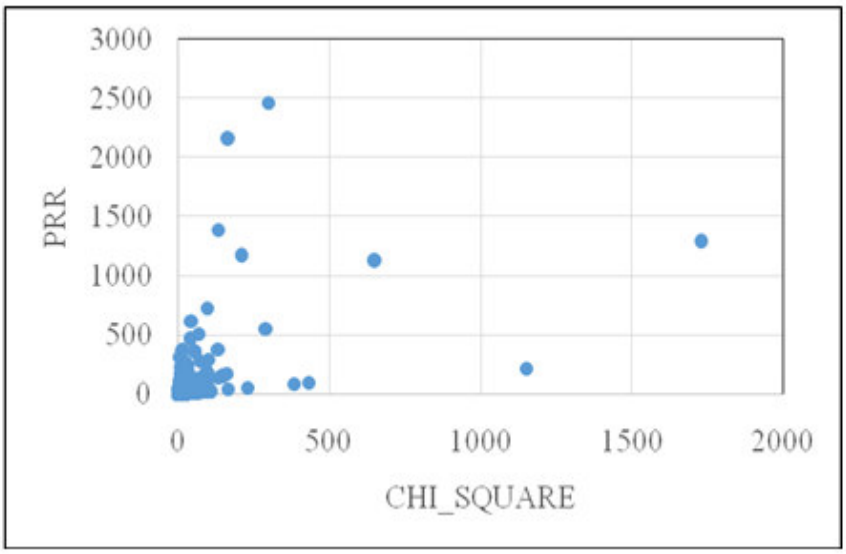

Figure 2
Plot of Chi_square and PRR

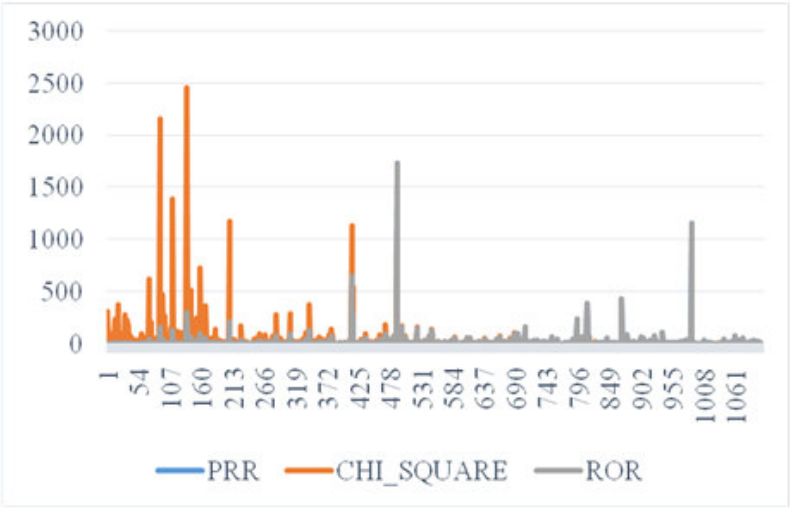

Figure 3
Plot of PRR, Chi_square and ROR

Table 3
Occurrence of adverse events

S. no	occurrences	Adverse Event	S.no	occurrences	Adverse Event	S.no	occurrences	Adverse Event
1	2148	Gastrointestinal disorder	51	140	Migraine	101	70	Convulsion
2	2140	Drug ineffective	52	140	Dyspepsia	102	69	Liver function test abnormal
3	1898	Rectal discharge	53	140	Nasopharyngitis	103	68	Abdominal pain lower
4	1696	Weight increased	54	137	Change of bowel habit	104	68	Gastric disorder
5	1618	Constipation	55	137	Product quality issue	105	67	Cerebrovascular accident
6	1374	Flatulence	56	137	Hypersensitivity	106	64	Tremor
7	1254	Diarrhoea	57	134	Menstrual disorder	107	64	Nervousness
8	1033	Abdominal pain upper	58	132	Pyrexia	108	64	Pneumonia
9	964	Steatorrhoea	59	132	Pollakiuria	109	63	Anal haemorrhage
10	900	Headache	60	129	Urticaria	110	62	Eating disorder
11	878	Abdominal distension	61	127	Pain in extremity	111	61	Premenstrual syndrome
12	770	Nausea	62	125	Abnormal faeces	112	61	Abortion spontaneous
13	661	Malaise	63	121	Nephrolithiasis	113	61	Cough
14	608	Pharmaceutical complaint	64	120	Fluid retention	114	60	Alanine increased
15	499	Abdominal pain	65	118	Oedema peripheral	115	59	Hypoaesthesia
16	484	Dizziness	66	115	Loss of consciousness	116	59	Dysgeusia
17	479	Frequent bowel movements	67	115	Hyperphagia	117	58	Cholecystectomy
18	448	Fatigue	68	114	Frustration	118	57	Bronchitis
19	397	Muscle spasms	69	107	Pancreatitis	119	57	Weight decreased
20	384	Vomiting	70	101	Nonspecific reaction	120	56	Musculoskeletal pain
21	380	Rectal haemorrhage	71	100	Abdominal discomfort	121	56	Adverse drug reaction
22	365	Faeces discoloured	72	99	Hypertension	122	56	Haemorrhoids
23	336	Pain	73	99	Hyperhidrosis	123	56	Condition aggbravated
24	306	Weight fluctuation	74	97	Influenza	124	55	Renal failure acute
25	290	unexpected Thera -peutic response	75	97	Discomfort	125	55	Lipiduria
26	284	Hunger	76	95	Dehydration	126	54	Irritable bowel syndrome
27	281	Feeling abnormal	77	95	Menstruation irregular	127	54	Chest discomfort
28	269	Haematochezia	78	94	Alopecia	128	53	Swelling
29	265	Food craving	79	94	Infrequent bowel movements	129	53	Diabetes mellitus
30	261	Asthenia	80	93	Decreased appetite	130	53	Sinusitis
31	250	Dyspnoea	81	91	Fall	131	52	Syncope
32	239	Anorexia	82	90	Myocardial infarction	132	52	Cellulitis
33	224	Ill-defined disorder	83	90	Palpitations	133	50	Breast cancer
34	221	Faecal incontinence	84	87	Stress	134	50	Respiratory tract infection
35	218	Insomnia	85	86	Death	135	50	Energy increased
36	212	Back pain	86	86	Menstruation delayed	136	49	Hypothyroidism
37	201	Adverse event	87	85	Increased appetite	137	49	Menorrhagia
38	200	Defaecation urgency	88	84	Diverticulitis	138	49	Pancreatitis acute
39	195	Rash	89	84	Error in Drug administration	139	49	Erythema
40	194	Anxiety	90	83	Myalgia	140	49	Vision blurred
41	194	Chest pain	91	82	Gallbladder disorder	141	49	Anaemia
42	178	Treatment noncompliance	92	81	Fear	142	48	Gastrointestinal pain
43	168	Stomach discomfort	93	79	Drug in pregnancy	143	48	Type 2 diabetes mellitus
44	162	Hepatic enzyme increased	94	78	Blood pressure increased	144	48	Joint swelling
45	155	Arthralgia	95	77	Asthma	145	48	Sleep disorder
46	150	Cholelithiasis	96	76	Gastrointestinal abnormal	146	48	Intentional drug misuse
47	149	Drug interaction	97	74	Chromaturia	147	48	Depressed mood
48	147	Depression	98	73	Somnolence	148	48	Neck pain
49	142	Gastroenteritis viral	99	73	Vaginal haemorrhage	149	47	Feeling cold
50	141	Pruritus	100	72	Thirst	150	47	Gastrooesophageal reflux disease

S. no	occurrences	Adverse event	S.no	occurrences	Adverse event	S.no	occurrences	Adverse event
151	47	Heart rate increased	201	32	Limb injury	251	24	Infection
152	46	Emotional disorder	202	32	Back disorder	252	24	Kidney infection
153	46	Irritability	203	32	Acne	253	24	Transient ischaemic attack
154	46	Joint injury	204	31	Influenza like illness	254	24	Appendicitis
155	45	Urinary tract infection	205	31	Lip swelling	255	24	Anorectal discomfort
156	45	Obsessive thoughts	206	31	Arthropathy	256	23	Overdose
157	45	Blood glucose decreased	207	31	Feeling hot	257	23	Intestinal functional disorder
158	45	Colitis	208	30	Vertigo	258	23	Rash macular
159	44	Sluggishness	209	30	Suicidal ideation	259	23	Dysmenorrhoea
160	44	Pharyngolaryngeal pain	210	30	Subcutaneous abscess	260	23	Mobility decreased
161	43	Liver injury	211	30	Obesity	261	23	Muscle tightness
162	42	Aspartate aminotransferase	212	30	Deep vein thrombosis	262	23	Burning sensation
163	42	Chills	213	30	Swelling face	263	23	Sinus headache
164	42	Binge eating	214	29	Viral infection	264	23	Gastritis
165	42	Hypoglycaemia	215	29	Cardiac failure congestive	265	23	Food poisoning
166	41	Rash pruritic	216	29	Lethargy	266	23	Bowel movement irregularity
167	41	Presyncope	217	28	Blood urine present	267	22	Eructation
168	41	Dry mouth	218	28	Road traffic accident	268	22	Cholecystitis acute
169	41	Renal pain	219	28	Confusional state	269	22	Multiple allergies
170	41	Hot flush	220	28	Sensation of heaviness	270	22	Jaundice
171	41	Thyroid disorder	221	28	Salt craving	271	22	Lower respiratory tract infection
172	40	Epilepsy	222	27	Renal impairment	272	22	Blood bilirubin increased

173	40	Metrorrhagia	223	27	Dysphagia	273	22	Lactic acidosis
174	39	Depressed consciousness	224	27	Skin odour abnormal	274	22	Blood alkaline phosphatase
175	39	Hypotension	225	27	Infected cyst	275	22	Malabsorption
176	39	Intestinal obstruction	226	27	Initial insomnia	276	22	Sunburn
177	39	Thrombosis	227	26	Haematemesis	277	22	Limb discomfort
178	39	Liver disorder	228	26	Colitis ulcerative	278	22	Blood pressure decreased
179	38	Blood triglycerides increased	229	26	Faecal decreased	279	22	Painful defaecation
180	38	Pruritus generalised	230	26	Polymenorrhoea	280	22	Self-injurious ideation
181	38	Faeces pale	231	26	Dry skin	281	21	Gastric ulcer
182	38	Renal failure	232	26	Cholecystitis	282	21	Cataract
183	37	Hepatitis	233	25	Eye pain	283	21	Epistaxis
184	37	Haemorrhage	234	25	Ankle fracture	284	21	Musculoskeletal discomfort
185	37	Blood glucose increased	235	25	Circulatory collapse	285	21	Cystitis
186	37	Atrial fibrillation	236	25	Feeling jittery	286	21	Musculoskeletal chest pain
187	36	Eye swelling	237	25	Swollen tongue	287	21	Dysuria
188	36	Cardiac disorder	238	25	Tachycardia	288	21	Eye disorder
189	36	Emotional distress	239	25	Hepatic failure	289	21	Dysarthria
190	35	Paraesthesia	240	25	Haemorrhage	290	21	Mood altered
191	35	Rash generalised	241	25	Vaginal discharge	291	21	Oropharyngeal blistering
192	35	Faeces hard	242	25	Back injury	292	21	Diarrhoea haemorrhagic
193	35	Gait disturbance	243	25	Oedema	293	21	Lung disorder
194	34	Proctalgia	244	25	Nocturia	294	21	Mental disorder
195	34	Poor quality sleep	245	25	Surgery	295	20	Throat tightness
196	34	Blood cholesterol increased	246	25	Nerve compression	296	20	Arrhythmia
197	33	Hepatic steatosis	247	24	Blood potassium decreased	297	20	Nephropathy
198	33	Joint sprain	248	24	Urine odour abnormal	298	20	Balance disorder
199	33	Pulmonary embolism	249	24	Skeletal stiffness	299	20	Rash erythematous
200	32	Angina pectoris	250	24	Coagulopathy	300	20	Local swelling

The results obtained for SQL query on the extracted data for count above 50 is shown in Table 3

SQL query

```
SELECT REAC.PT, COUNT(REAC.PT), COUNT(DISTINCT REAC.ISR) FROM DRUG, REAC WHERE
(DRUG.ISR=REAC.ISR) AND (DRUG.DRUGNAME="ORLISTAT") GROUP BY REAC.PT ORDER BY
COUNT(REAC.PT) DESC;
```

Table 3
Result of Query showing the COUNT of ADR due to Orlistat

ADVERSE EVENTS	COUNT(REAC.PT)	COUNT(DISTINCT REAC.ISR)
Drug interaction	90	88
Diarrhoea	87	81
Abdominal pain	70	67
Dizziness	58	57
Fall	58	57
Renal failure acute	57	57
Nausea	56	55
Chest pain	55	49
Myocardial infarction	51	46
Vomiting	51	48

CONCLUSIONS

Childhood obesity is a grave problem and high incidence of adverse event could be due to some other drug interaction which the patient may be taking. Many adverse health effects associated with adult obesity have been statistically analyzed and side effects seem to be very alarming. Analysis showed different types of adverse effects which will lead to new, safe anti-obesity drugs in the near future. The EHT algorithm for creating the model was robust in analyzing the 2058 classes available and based on which the query results were obtained for different adverse effects.

CONFLICT OF INTEREST

Conflict of interest declared none.

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We sincerely thank the above reviewers for peer reviewing the manuscript