

White Paper

SINGULAIR: SAFETY SIGNAL DETECTION BASED ON AERS DATA

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Abstract

Singulair has been brought under the scanner of the United States Food and Drug Administration (US FDA) in the context of adverse events related to suicide and mood and behavioral changes. In this paper we explore this association using retrospective data that is publicly available (US FDA Adverse Events database) and using quantitative methods of safety signal detection. Different measures of signal detection are discussed, along with a qualitative comparison of the methods.

A few select measures are applied to assess the association between Singulair and adverse events related to suicide and mood and behavioral changes. This analysis does not suggest an increased risk of suicidal behavior or mood changes with the use of Singulair.

Results are also discussed at the Preferred Term (PT) level. An in-depth investigation of the adverse event reports is required to comment on medical relevance of this analysis.

Keywords:

drug safety, pharmacovigilance, FDA AERS, Singulair, signal detection, Bayesian data - mining

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1. INTRODUCTION

Singulair has recently come under attention of the United States Food and Drug Administration (US FDA) for adverse events related to suicide (viz. suicidal ideation, suicide attempt, completed suicide etc.) and mood change. To investigate this association, we looked at the FDA AERS data from Q1 2004 through Q3 2007 that is available on the US FDA website. The data for Singulair for all 15 quarters were analyzed for several behavioral Preferred Terms (PTs) selected on the basis of their relationship with suicidal and mood related behavior.

The US FDA is evaluating a recently committed suicide event in detail. During the clinical development approximately 11,000 patients were enrolled in 40 Singulair clinical trials. Merck officials have stated that there was no case of committed suicide during these trials. Singulair is used by millions of patients in the U.S, according to Merck. First approved in 1998, it's part of a class of asthma and allergy drugs that includes Astra Zeneca's Accolate and Critical Therapeutics' Zylfo.

In this paper, we present a brief introduction to various statistical methodologies that are generally used to detect signals in a safety database. We will compare results on adverse events related to suicidal behavior and mood change-related PTs reported against Singulair. Statistical tools for safety signal detection enable numerical analysis of data. However, a comprehensive medical analysis of the adverse events is required to interpret statistical inference in a meaningful manner. Due to limitation of what is available in the FDA AERS database, it is not possible to conduct a thorough analysis of the adverse events. Nevertheless, any signal detected using statistical techniques would suggest a need for further investigation.

Section 2 has a brief discussion about statistical safety data mining methods. Description of the data is presented in Section 3. Finally, discussion of the analysis is provided in Section 4.

2. MATERIALS AND METHODS

The history of safety signal detection does not go back a long way, though most of the commonly used statistical methods are classical in nature. Refer to Van Puijenbroek (2001) for details. However, some methods which are developed more recently, exploit the powerful inference techniques from Bayesian Statistics (refer to DuMouchel (1999), Genkin *et. al.* (2007), Bates *et. al.* (1998)). Here is a brief introduction about the statistical techniques that are used in the safety data mining.

With all classical techniques, we evaluate the data in the safety database on a case by case basis. For a fixed drug and for a fixed adverse event (AE) combination, suppose it is possible to construct a 2x2 contingency table as in Table 1.

The fundamental idea behind safety data mining is to find the significance of the count '*a*', since the total number of drug-event combinations ($N = a + b + c + d$) is large.

Table 1: 2x2 contingency table for a particular drug and a particular AE

DRUG \ AE	AE under study	Other AEs
Drug under study	<i>a</i>	<i>b</i>
Other drugs	<i>c</i>	<i>d</i>

Statistical interpretation of this objective is that we want to find whether different levels of the attribute DRUG are independent of the AE.

We describe below four classical methods, based on frequentist principles, and two methods based on the Bayesian approach.

The simplest and most widely used measure is known as Proportional Reporting Ratio (PRR). Given a 2x2 contingency table, PRR can be calculated from the following expression.

$$PRR = \frac{a/(a+b)}{c/(c+d)}$$

The interpretation of *PRR* is that it is the ratio of probability of the occurrence of the AE while on the drug under study to probability of occurrence while on any other drug. So a unit value of *PRR* will indicate independence. An approximate 95% confidence interval for *PRR* is calculated as follows:

$$95\% CI = \exp\left(\ln(PRR) \pm 1.96 \sqrt{\left(\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}\right)}\right)$$

In practice, based on how statistical significance is generally defined for relative risks, if the lower confidence limit of *PRR* is greater than 1, it could be interpreted as suggestive of a possible signal.

Another simple method along the same lines is called Reporting Odds Ratio (*ROR*). *ROR* is defined as (given the 2x2 contingency table):

$$ROR = \frac{ad}{bc}$$

An *ROR* value is interpreted almost in the same way as it is done for *PRR*. Instead of ratio of probabilities, an *ROR* value gives us the ratio of odds. A 95% confidence interval is calculated as follows:

$$95\% CI = \exp\left(\ln(ROR) \pm 1.96 \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}\right)$$

Decision making criteria using an *ROR* is same as that of *PRR*.

A Chi-squared test of independence between two attributes is very popular. Yates' correction to the Chi-squared test is used to minimize the approximation error due to low cell frequencies. The independence of two attributes is taken as a null hypothesis and the test statistics under the null hypothesis can be calculated using the following expression:

$$\chi^2 = \sum \frac{(O-E)^2 - 0.5}{E}$$

where the summation is taken over four cells and *O* denotes the observed frequency while *E* denotes the expected frequency for each cell. For example, for the cell (1, 1), i.e., the cell corresponding to the first row and first column,

$$O = a, \quad E = \frac{(a+b)(a+c)}{(a+b+c+d)},$$

and so on. An approximate *p*-value can be calculated using the right tail of the χ^2 -distribution with 1 degree of freedom. The decision about whether a signal exists can be made on the basis of the *p*-value given a pre-specified level of significance.

A way to measure association between two attributes is called Yule's *Q*. The expression for calculating *Q* is given by

$$Q = \frac{ad - bc}{ad + bc}$$

The range of *Q* is [-1, +1] with zero being the value for independence. A 95% confidence interval for *Q* is calculated as follows:

$$95\% CI = Q \pm 1.96 \frac{(1-Q^2)}{2} \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}$$

Another way is to fit a Poisson distribution to the count in (1, 1) cell. The probability of getting a count of at least *a* in the (1, 1) cell could serve as a good way to detect extraordinary cell count.

All these methods are based on a 2x2 contingency table wherein a particular drug-event combination is considered. This is inconvenient when we are interested in many such combinations. The following methods, which are based on Bayesian inferential techniques, provide solutions considering all the reported drug-event combinations at a time.

Suppose we have the following representation of the data as given in Table 2.

Table 2: Table showing all drug-event combinations

Drug	Adverse Drug Reactions				Total
	AE 1	...	AE <i>j</i>	...	
Drug 1
...			.		.
Drug <i>i</i>	<i>C_{ij}</i>	...	<i>C_{i.}</i>
...			.		.
...			.		.
Total	<i>C_{.j}</i>	...	<i>C</i>

Information Component (*IC*) analysis is a method that uses Bayesian statistical principles to quantify apparent dependencies in a dataset. The measure of disproportionality used in the Bayesian Confidence Propagating Neural Network (BCPNN), is referred to as the Information Component (*IC*) because of its derivation from measures used in Information Theory. A confidence interval is calculated for the *IC* of each combination. The expectation and variance of *IC* values for each (*i, j*)-th cell are given by

$$E(IC_{ij}) = \log_2 \frac{(c_{ij} + \gamma_{ij})(C + \alpha)(C + \beta)}{(C + \gamma)(c_i + \alpha_i)(c_j + \beta_j)},$$

$$V(IC_{ij}) = \frac{1}{(\log 2)^2} \left[\frac{C - c_{ij} + \gamma - \gamma_{ij}}{(c_{ij} + \gamma_{ij})(1 + C + \gamma)} + \frac{C - c_i + \alpha - \alpha_i}{(c_i + \alpha_i)(1 + C + \alpha)} + \frac{C - c_j + \beta - \beta_j}{(c_j + \beta_j)(1 + C + \beta)} \right]$$

Where

$$\gamma = \gamma_{ij} \frac{(C + \alpha)(C + \beta)}{(c_i + \alpha_i)(c_j + \beta_j)}$$

And $\gamma_{ij} = 1, \alpha_i = 1, \alpha = 2, \beta_j = 1, \beta = 2, C$ is the total number of reports in the database, C_{ij} the number of combinations between a specific drug [*i*] and the suspected AE [*j*], c_i the total number of reports on drugs [*i*] in the database and c_j the total number of reports on the suspected AE [*j*] in the database.

To make a decision about any drug-event combination, the lower 95% confidence limit of the *IC* value is monitored. It is approximately computed as follows:

$$E(IC) - 2\sqrt{V(IC)},$$

and is denoted by “*IC-2SD*”. *IC* value being zero can be interpreted as independence between two attributes viz. drug and AE. For any drug-event combination, if *IC-2SD* > 0 then it may be considered to suggest a possible signal.

Another Bayesian method that is sometimes used is called Empirical Bayes Geometric Mean (*EBGM*), which is based on the concept of Multi-gamma Poisson Shrinkage (*MGPS*). In summary, this approach involves finding the posterior distribution of the relative risk (observed/expected) with some prior assumption. Given the posterior distribution, following notations of DuMouchel (1999), the expectation of the logarithm

(base 2) of the relative risk is found. For any (*i, j*)-th cell, let us denote it by $EB \log_2 ij$. Then *EBGM* is defined as

$$EBGM_{ij} = 2^{EB \log_2 ij}$$

An *EBGM* value can be interpreted in the same way as a relative risk value. For example, if the *EBGM* = 3.9 for a particular drug-event combination, then this drug-event combination occurred in the data 3.9 times more frequently than expected.

EB05 and *EB95* are the lower and upper bounds of the two-sided 90% credible interval around *EBGM*.

$$EB05 \approx EBGM_{ij} \exp \left\{ -1.645 / \sqrt{(c_{ij} + 1)} \right\}$$

$$EB95 \approx EBGM_{ij} \exp \left\{ 1.645 / \sqrt{(c_{ij} + 1)} \right\}$$

Data mining threshold using *EBGM* is *EB05* > 2 i.e. when the drug-event combination occurs at least twice as often as expected.

Using the Bayesian approach, there is another way to analyze the data based on hierarchical Bayesian modeling. In this approach, a logistic regression model is fitted to the data with two possible priors. When Laplace prior is used for the model parameters, it is known as LASSO logistic regression and when a Gaussian prior is used, it is known as Ridge logistic regression. These are more recent methods being tried by some researchers. These are not yet commonly used as the methods of choice. We have mentioned these here only for completeness of the discussion. We will not apply these methods to the data.

In this paper, our primary aim is to determine the safety profile of Singulair on the basis of US FDA AERS data for mood and suicidal behavior AEs using three measures, namely, *PRR*, *IC* and *EBGM*. We have chosen *PRR* as being representative of the frequentist methods since it is the most widely used and accepted measure. We have chosen *IC* and *EBGM* since these are the two methods based on Bayesian inferential techniques that are well-researched and are also included in available commercial software.

3. RESULTS

In this section, we present summary from the US FDA AERS data from 2004 Q1 through 2007 Q3. The data are summarized on the basis of the PTs related to suicidal behavior and mood change. Statistical analyses are

presented using the three safety data mining methods mentioned above.

In all our analysis, we looked at Individual Safety Reports (ISR) and only the initial reports, since follow-up reports would increase the multiplicity in number of records without adding any further information.

Table 3.1: Table showing the preferred terms considered in the analysis

ACCOMPLISHED SUICIDE	EMOTIONAL DISTURBANCE NOS	MOROSE
ANHEDONIA	FEELING BLUE	MOROSENESS
ATTEMPTED SUICIDE	FEELING DOWN	NEGATIVE THOUGHTS
COMPLETED SUICIDE	FEELING GUILTY	REDUCED INTEREST IN USUAL ACTIVITIES
CRYING	FEELING OF DESPAIR	SELF MUTILATION
DEATH WISHES	FEELING REMORSE	SELF-INJURIOUS IDEATION
DECREASED INTEREST	FEELING SAD	SINKING FEELING
DELIBERATE SELF-HARM	FRUSTRATION	SUICIDAL BEHAVIOUR
DELIBERATE SELF-INJURY	HIGH-PITCHED CRYING	SUICIDAL IDEATION
DEPRESSED MOOD	INTENTIONAL SELF-INJURY	SUICIDAL TENDENCY
DEPRESSIVE SYMPTOM	LIFE WEARINESS	SUICIDE
DEPRESSIVE SYMPTOM AGGRAVATED	LOSS OF ALL INTEREST	SUICIDE ATTEMPT
DISTRESS	LOSS OF ALL PLEASURE	SUICIDE ATTEMPT BY DRUG OVERDOSE
DISTRESS COMPLAIN INCREASED	LOSS OF INTEREST	SUICIDE ATTEMPT OTHER THAN OVERDOSE
DYSPHORIA	LOW MOOD	TEARFULNESS
EMOTIONAL DEJECTION	MOOD ALTERED	THOUGHTS OF SELF HARM
EMOTIONAL DISORDER	MOOD DEPRESSION	UNHAPPINESS
EMOTIONAL DISTRESS		

For data summarization (Section 3.1) and for statistical analyses (Section 3.2), we consider all records that involved Singulair, as primary or secondary suspect drug, or as concomitant treatment.

Following preferred terms (PTs) may be related to suicidal behavior and mood change. These PTs may be considered to cause someone to commit or think of

committing suicide (Table 3.1). In addition to these PTs, we will also analyze the PT of Abnormal Behavior. In our assessment, we do not consider this PT as related to suicidal behavior and mood change, but since it is related to behavior and may also be considered as related to mood by some, we will analyze this PT separately. Thus this PT will also be included in the descriptive summary of the AERS data.

Table 3.1.1: Table showing the summary of AEs based on ISR

PT	TOTAL # OF ISRs	# OF ISRs with DRUG-EVENT COMBINATIONS	% OF ISRs with DRUG-EVENT COMBINATIONS	# OF ISRs CONFIRMED MEDICALLY	% OF ISRs CONFIRMED MEDICALLY
ABNORMAL BEHAVIOUR	4054	46	1.13468	20	0.49334
ANHEDONIA	529	1	0.18904	1	0.18904
COMPLETED SUICIDE	7792	4	0.05133	3	0.0385
CRYING	2516	35	1.3911	11	0.4372
DECREASED INTEREST	285	4	1.40351	1	0.35088
DEPRESSED MOOD	1160	14	1.2069	5	0.43103
DEPRESSIVE SYMPTOM	124	0	0	.	.
DYSPHORIA	145	0	0	.	.
EMOTIONAL DISORDER	1050	8	0.7619	4	0.38095
EMOTIONAL DISTRESS	1299	7	0.53888	4	0.30793
FEELING GUILTY	47	1	2.12766	1	2.12766
FEELING OF DESPAIR	189	2	1.0582	.	.
FRUSTRATION	100	0	0	.	.
HIGH-PITCHED CRYING	6	0	0	.	.
INTENTIONAL SELF-INJURY	566	4	0.70671	.	.
MOANING	85	1	1.17647	1	1.17647
MOOD ALTERED	1070	9	0.84112	4	0.37383
MOROSE	6	0	0	.	.
NEGATIVE THOUGHTS	72	0	0	.	.
SELF INJURIOUS BEHAVIOUR	286	4	1.3986	2	0.6993
SELF MUTILATION	135	1	0.74074	1	0.74074
SELF-INJURIOUS IDEATION	295	2	0.67797	2	0.67797
SUICIDAL BEHAVIOUR	115	3	2.6087	2	1.73913
SUICIDAL IDEATION	5577	29	0.51999	8	0.14345
SUICIDE ATTEMPT	4808	11	0.22879	7	0.14559
TEARFULNESS	251	1	0.39841	0	.

3.1 Summary of Data

To summarize the data, we provide the number and percentages of reported drug-event combinations and also provide the same summary for all medically confirmed drug-event combinations.

We also provide summary in terms of ISRs. Table 3.1.1 and Table 3.1.2 provide these summaries. In Table 3.1.1, while calculating the percentages, the denominator is the total number of corresponding PTs reported during the given time period.

Table 3.1.2: Table showing the summary of AEs based on Cases

PT	TOTAL # OF CASES	# OF CASES with DRUG-EVENT COMBINATIONS	% OF CASES with DRUG-EVENT COMBINATIONS
ABNORMAL BEHAVIOUR	3939	46	1.16781
ANHEDONIA	524	1	0.19084
COMPLETED SUICIDE	7413	4	0.05396
CRYING	2444	35	1.43208
DECREASED INTEREST	280	4	1.42857
DEPRESSED MOOD	1118	14	1.25224
DEPRESSIVE SYMPTOM	120	0	0
DYSPHORIA	139	0	0
EMOTIONAL DISORDER	1028	8	0.77821
EMOTIONAL DISTRESS	1233	7	0.56772
FEELING GUILTY	46	1	2.17391
FEELING OF DESPAIR	186	2	1.07527
FRUSTRATION	98	0	0
HIGH-PITCHED CRYING	6	0	0
INTENTIONAL SELF-INJURY	549	4	0.7286
MOANING	84	1	1.19048
MOOD ALTERED	1043	9	0.8629
MOROSE	6	0	0
NEGATIVE THOUGHTS	72	0	0
SELF INJURIOUS BEHAVIOUR	280	4	1.42857
SELF MUTILATION	135	1	0.74074
SELF-INJURIOUS IDEATION	287	2	0.69686
SUICIDAL BEHAVIOUR	109	3	2.75229
SUICIDAL IDEATION	5375	29	0.53953
SUICIDE ATTEMPT	4591	11	0.2396
TEARFULNESS	243	1	0.41152

3.2 Statistical Analysis

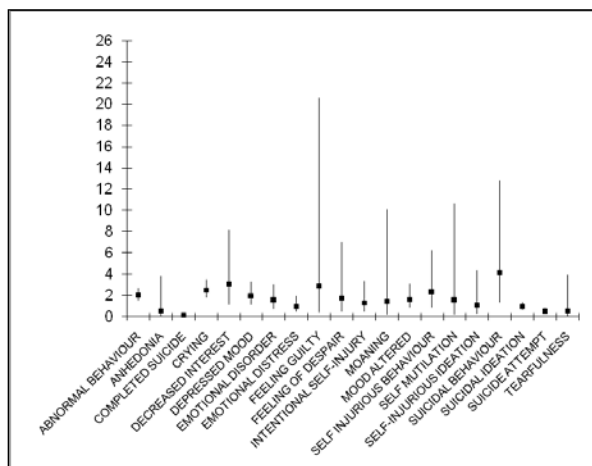
We first find the *PRR* values for the combination of Singulair and all adverse events (mentioned in Table 3.1) combined. The *PRR* value, pooled for all PTs related to suicidal behavior and mood changes listed above, is found to be 0.99 and the corresponding 95% confidence interval as (0.86,1.16).

The *PRR* values for the combination of Singulair and the reported PTs from Table 3.1 with their 95% confidence intervals are presented in the Table 3.2.1 and shown graphically in Figure 3.2.1. Results corresponding to the PT of Abnormal Behavior are also presented as mentioned above. For the other two methods only graphical presentation is included.

Table 3.2.1: Table showing the PRR values with 95% confidence intervals

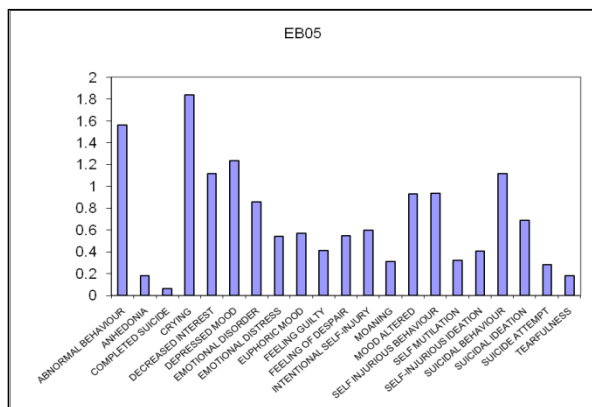
PT	Number of drug-event combinations	PRR	Lower Limit	Upper Limit
ABNORMAL BEHAVIOUR	46	2.00407	1.50082	2.6761
ANHEDONIA	1	0.53671	0.07553	3.8137
COMPLETED SUICIDE	4	0.10906	0.04093	0.2906
CRYING	35	2.47328	1.775	3.4463
DECREASED INTEREST	4	3.05187	1.14238	8.153
DEPRESSED MOOD	14	1.9421	1.14935	3.2816
EMOTIONAL DISORDER	8	1.49402	0.74655	2.9899
EMOTIONAL DISTRESS	7	0.91798	0.43741	1.9265
FEELING GUILTY	1	2.88232	0.40392	20.5677
FEELING OF DESPAIR	2	1.74323	0.43503	6.9853
INTENTIONAL SELF-INJURY	4	1.24516	0.46685	3.3211
MOANING	1	1.41864	0.19933	10.0966
MOOD ALTERED	9	1.5877	0.82544	3.0539
SELF INJURIOUS BEHAVIOUR	4	2.32554	0.87107	6.2086
SELF MUTILATION	1	1.49249	0.20968	10.6236
SELF-INJURIOUS IDEATION	2	1.07447	0.26837	4.3019
SUICIDAL BEHAVIOUR	3	4.11656	1.32211	12.8174
SUICIDAL IDEATION	29	0.91118	0.63318	1.3112
SUICIDE ATTEMPT	11	0.41966	0.23239	0.7578
TEARFULNESS	1	0.5486	0.0772	3.8983

Figure 3.2.1: Figure showing the PRR values with confidence intervals



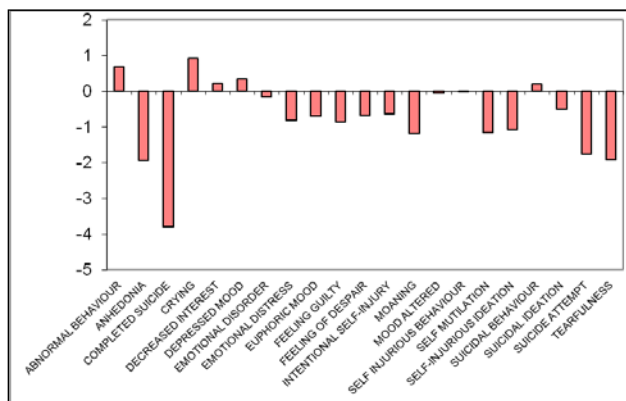
The EB05 values obtained from the EBGm method are shown in the Figure 3.2.2.

Figure 3.2.2: Figure showing the EB05 values



Using IC method lower (IC-2SD) 95% confidence limits of IC values are shown in Figure 3.2.3.

Figure 3.2.3: Figure showing the IC-2SD values



4. DISCUSSION

Overall, these data, pooled across relevant PTs, do not suggest an increased risk of suicidal behavior or mood change associated with use of Singulair based on the results of the statistical methods used. It is likely that pooling a number of PTs may mask a signal. Hence we also analyzed individual PTs.

When we look at the analysis for individual PTs, Abnormal Behavior, Crying, Decreased Interest, Depressed Mood and Suicidal Behavior are the PTs that may suggest increased risk. The general practice in signal detection is to consider 5% level of significance for PRR and IC, and to consider 10% level of significance for EBGm. So we have used these significance levels in our analysis and comparisons. However, we have confirmed that the statistical significance for these 5 PTs is unaltered even when we use 10% level of significance for PRR and IC. Also, as mentioned in Section 2, the threshold of 2.0 is often used for EB05 in signal detection. However, given that the analysis we have presented here is exploratory and descriptive in nature, we apply to EBGm the standard definition of statistical significance that is used for any relative risk, i.e., lower bound of the confidence interval being greater than 1.0.

The PRRs for these 5 PTs are at or above 1.9, with PRRs for 4 PTs being 2.0 or above. The lower limit of the 95%

CI is greater than 1.0 for all 5 PTs. The other 2 methods of IC and Empirical Bayes yield results that are remarkably similar to the conclusions based on PRR. The lower bound of the 90% CI with the Empirical Bayes method is greater than 1.0 for these 5 PTs, and the lower bound of the 95% CI with the IC methods is greater than 0 for these 5 PTs. Using the standard definition of statistical significance for the 3 methods we have considered, it appears that Singulair may be associated with an increased risk of Abnormal Behavior, Crying, Decreased Interest, Depressed Mood and Suicidal Behavior, though the evidence of association may not be as strong as is required for detecting a signal. We also need to take cognizance of the issue of multiple comparisons. Since we have simultaneously analyzed 19 PTs that had at least one occurrence, based on the same set of data, it is possible that some PT would result in statistical significance purely by chance. However, our analysis is exploratory in nature, not confirmatory, and we have not made any adjustment for multiple comparisons.

Bayesian methods are generally more specific and less sensitive as compared to frequentist methods. In general, Bayesian methods highlight fewer signals than frequentist methods due to the statistical shrinkage associated with low reporting frequencies that is applied in the Bayesian methods (Hauben et al., 2005). Also, in general, frequentist methods seem to work well (at least in terms of asymptotic properties) when the cell frequencies are large. In the context of safety data mining, low cell count is a common phenomenon. In such scenarios, we cannot rely on asymptotic properties of PRR and other frequentist methods. On the other hand, the main drawback of the Bayesian methods (especially using IC method) is the assumption of symmetric posterior probability interval. But Van Puijenbroek (2001) has suggested that the performance of frequentist methods is similar to that of the IC method when the cell count for a drug-AE combination is at least 4. The only concern that can be raised about EBGM is the use of subjective prior, though the prior is quite robust and it reduces the computational burden to a large extent.

For the data we have analyzed, the number of reports for the 5 PTs of Abnormal Behavior, Crying, Decreased

Interest, Depressed Mood and Suicidal Behavior are 46, 35, 4, 14 and 3 respectively. Our observed agreement between the qualitative results of PRR, IC and EBGM corroborates what Van Puijenbroek (2001) has suggested to a large extent. However, we also observe an agreement between these methods for the PT of Suicidal Behavior although the number of cases is less than 4. Our qualitative results also corroborate the observation in Hauben et al. (2005).

5. CONCLUSION

Pooled across related PTs, these data do not suggest an increased risk of suicidal behavior or mood change with use of Singulair. We observed statistical significance with some measures and for some PTs. However, we recognize that it may be more meaningful to use different thresholds for the lower limits of confidence intervals of estimates in order to conclude significant association between a drug and an event. More importantly, medical relevance is critical in signal detection and is critical for meaningful interpretation of statistical significance. In order to comment on the medical relevance and significance of the statistical analysis, in-depth analysis of the data on the adverse event reports would be required. We are in the process of analyzing causal association at the individual case level, based on the limited data that are available in the AERS public domain.

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