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Age and disease severity predict choice of atypical neuroleptic: a signal detection approach to physicians' prescribing decisions

Jerome A. Yesavage[a,b,*], Jennifer Hoblyn[a,b], Javaid Sheikh[a,b], Jared R. Tinklenberg[a,b], Art Noda[b], Ruth O'Hara[b], Catherine Fenn[b], Martin S. Mumenthaler[b], Leah Friedman[b], Helena C. Kraemer[b]

[a]*Palo Alto Veterans Affairs Health Care System, 3801 Miranda Avenue, MC 151Y, Palo Alto, CA, USA*
[b]*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94304, USA*

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Abstract

Objective: We used a novel application of a signal detection technique, receiver operator characteristics (ROC), to describe factors entering a physician's decision to switch a patient from a typical high potency neuroleptic to a particular atypical, olanzapine (OLA) or risperidone (RIS). Methods: ROC analyses were performed on pharmacy records of 476 VA patients who had been treated on a high potency neuroleptic then changed to either OLA or RIS. Results: Overall 68% patients switched to OLA and 32% to RIS. The best predictor of neuroleptic choice was age at switch, with 78% of patients aged less than 55 years receiving OLA and 51% of those aged greater than or equal to 55 years receiving OLA ($\chi^2 = 38.2$, $P < 0.001$). Further analysis of the former group indicated that adding the predictor of one or more inpatient days to age increased the likelihood of an OLA switch from 78% to 85% ($\chi^2 = 7.3$, $P < 0.01$) while further analysis of the latter group indicated that adding the predictor of less than 10 inpatients days to age decreased the likelihood of an OLA switch from 51% to 45% ($\chi^2 = 7.0$, $P < 0.01$). Conclusions: ROC analyses have the advantage over other analyses, such as regression techniques, insofar as their "cut-points" are readily interpretable, their sequential use forms an intuitive "decision tree" and allows the potential identification of clinically relevant "subgroups". The software used in this analysis is in the public domain (http://mirecc.stanford.edu).
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1. Introduction

Since the introduction of the first neuroleptic chloropromazine in 1952, researchers and clinicians have continued to improve both the efficacy and the tolerability of these medications. These medications are used to treat psychotic symptoms across a spectrum of disorders including schizophrenia, mood disorders, and dementias. The costs of treating schizophrenia alone have been estimated to be between \$33 and \$65 billion annually (Rice, 1999; Wyatt et al., 1995). Since the 1980′s we have seen the development of newer atypical agents which have been reported to have greater efficacy in the treatment of negative symptoms, maintenance of response, as well as a lower incidence of extrapyramidal symptoms compared to typical agents.

Physician prescribing practices of atypical neuroleptics have come under scrutiny because of the high cost of these compounds (between \$3000 and \$7000 per year) compared to traditional neuroleptics (approximately \$300 per year for haloperidol; Brown et al., 1999; Markowitz et al., 1999). To assist clinical decision-making and develop health policy, we used a novel signal detection technique, receiver operator characteristics (ROC) to identify factors entering a physician's decision to switch a patient from a typical neuroleptic to a particular atypical, olanzapine (OLA) or risperidone (RIS).

The Veterans Health Administration of the Department of Veterans Affairs (VA) treats tens of thousands

* Corresponding author. Tel.: +1-650-852-3287; fax: +1-650-852-3297.
E-mail address: yesavage@stanford.edu (J.A. Yesavage).

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of patients with neuroleptics each year and has been under considerable pressure to contain costs (Leslie & Rosenheck, 2001a). The effect of institutional fiscal stress on the use of atypical neuroleptic medications within the VA system has been studied using logistic regression techniques (Leslie & Rosenheck, 2001b). Using nationwide data for a 3-month period in 1999, this study found that over half the patients received an atypical neuroleptic, usually either olanzapine or risperidone. The authors were surprised to note that increased fiscal stress was associated with increased likelihood of receiving atypical antipsychotics, a result possibly consistent with those that have argued that atypical antipsychotics may be more cost-effective than typical neuroleptics (Fleischhacker, 1999). However, fiscal stress was associated with reduced likelihood of receiving the more expensive atypical neuroleptics (clozapine and olanzapine) but positively associated with receiving the least expensive atypical (risperidone). They concluded that institutional fiscal stress does not seem to reduce the broad availability of such medications but does affect which atypical physicians select.

The logistic regression techniques used in the Leslie and Rosenheck (Leslie & Rosenheck, 2001b) study suggested a number of other factors might influence the selection of a medication by the physician. For example, they found that age, number of hospitalizations, and race might also influence this choice. An advantage of the signal detection approach to such data is that it may be able to identify complex interactions of such effects as well as identifying specific cut-points at which a particular factor becomes most influential, for example, age older than 55 years. The following work is such an analysis in a VA pharmacy database.

2. Methods

2.1. Database

Based on pharmacy records of Veterans Affairs Palo Alto Health Care System (VAPAHCS) we studied records of 476 patients who had been treated for at least 28 days with a high potency neuroleptic and then were changed to either OLA or RIS, and took that particular atypical for at least 28 days. Predictors of choice of atypical included: age of patient at switch, gender, race and disease severity, as indexed by number of days of inpatient treatment cumulated prior to switch. Average age at switch of patients was 53.6 (13.2) years and 95% were male. In terms of racial/ethnic background: 64.9% were Caucasian, 13.7% African-American, 7.4% Hispanic, 3.6% Asian-American, 0.6% native American and 9.8% had unknown backgrounds. The average number of inpatient days before the switch was 12.2 days (84.5).

2.2. Statistical analysis

The first step in conducting a ROC analysis is to define the clinically relevant outcome criterion (specific outcome of interest), the "gold standard". In this case we defined our criterion as change to OLA rather than to RIS. Next, the ROC software searches all the predictor variables, for example, age of patient at switch, and their associated cut-points, for example, those patients aged less than 55 years versus those 55 years or older. Then the program identifies those with the optimal sensitivity and specificity for identifying those particular patients with the specific clinically relevant outcome (in this study, switch to OLA). In this study equal weight was given to false positives and negatives in determining optimal cut-points. The ROC software tests every predictor variable and every possible cut-point value for that variable for every subject in the database. Once the optimal predictor variable and associated cut-point are identified, the association with the outcome of interest is tested with a stopping rule (in the current study the rule is a 2×2 χ^2 test significant at less than the 1% level). If the association passes the rule the sample is divided into two groups according to performance on the optimal predictor variable and optimal cut-point. The ROC analysis is then restarted, separately, for each of the two sub-groups. The ROC procedure again examines every predictor variable for every subject and cut-point to see if either group can be further separated. The procedure will stop when it hits the stopping rule or when a subgroup has too small (less than 10) a sample size for further analysis. For further details regarding ROC analysis see Kraemer (1992). The final result is a decision tree (see Fig. 1 for actual output). The software used in this analysis was developed at the Sierra-Pacific MIRECC and is in the public domain (http://mirecc.stanford.edu).

3. Results

As illustrated in Fig. 1, overall 68% of the 476 patients were switched to OLA. Therefore, 32% switched to RIS. The ROC procedure found the best predictor of atypical neuroleptic choice was age of patient at switch, with 78% of patients aged less than 55 years receiving OLA compared with 51% of those aged greater than or equal to 55 years receiving OLA ($\chi^2=38.2$, $P<0.001$). Further ROC analysis of the aged less than 55 years group indicated that adding the predictor of one or more inpatient days to the predictor age at switch increased the likelihood of an OLA switch from 78 to 85% ($\chi^2=7.3$, $P<0.01$). Further analysis of the aged greater than or equal to 55 years group indicated that adding the predictor of less than 10 inpatient days to age decreased the likelihood of an OLA switch from 51 to 45% ($\chi^2=7.0$, $P<0.01$).

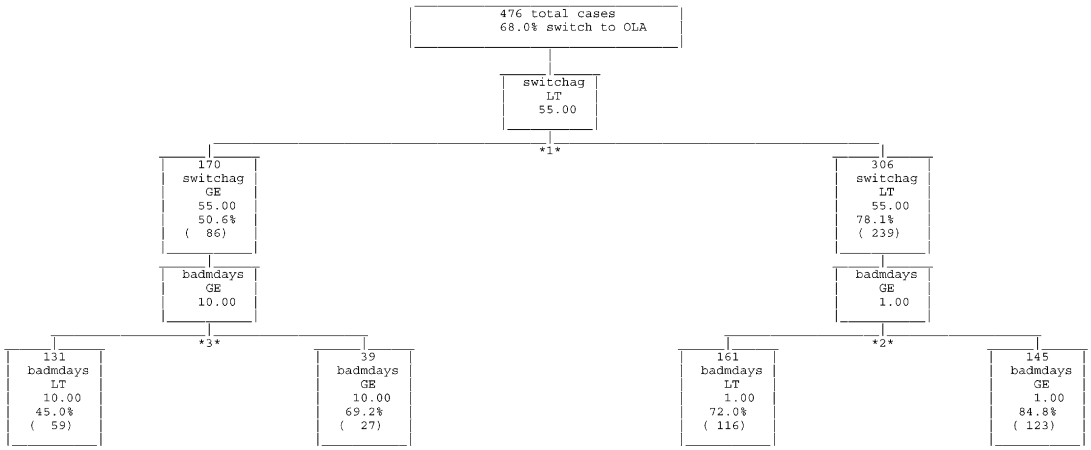

Fig. 1. Actual output of Decision Tree. The first box indicates the 476 total patients of whom 68.0% switched to OLA. The next box is the variable that was the best cut point for separating the OLA versus RIS switch (age at switch less than 55 years). This is the First cut point labeled "*1*". The total group of 476 would then be divided into two subgroups of 170 and 306 patients. Of the right hand selection of 306 subjects 78.1% or 239 actually switched to OLA. The next cut-point in this subgroup is labeled "*2*" and is inpatient days greater than or equal to 1. One then has the 306 patients divided into two more groups, one with 161 patients and the other with 145. The later group of 145 saw 123 or 84.8% change to OLA, and so on.

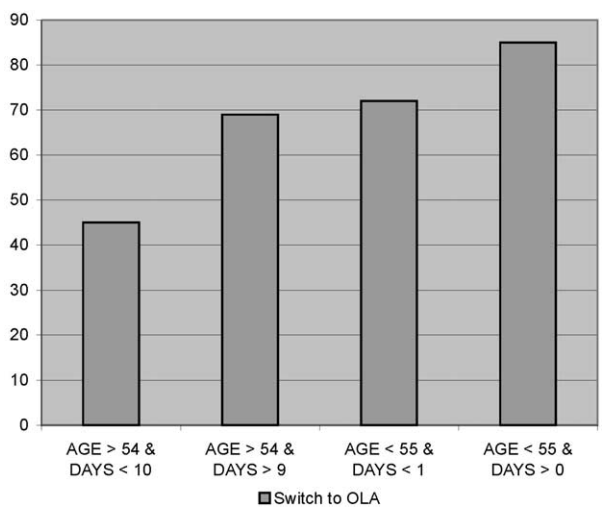

Fig. 2. Subgroups of patients switched to OLA versus RIS showing that four distinct subgroups may be identified with only two variables and three different cut-points for predictor variables.

4. Discussion

The results of the current study replicate the findings of Leslie and Rosenheck (2001a) regarding the importance of age and duration of inpatient treatment days as predictors of OLA choice. The signal detection methods, however, provides some additional useful information. For example, a specific age cut-point of 55 years is identified for optimal sensitivity and specificity of OLA choice. Furthermore, the signal detection analysis permits a more detailed understanding of the interaction of age with disease severity as indexed by length of inpatient stay. One sees, for example, that adding the predictor of one or more inpatient days to the patients greater than age 55 increased the likelihood of an OLA switch from 78 to 85%. But one also sees that adding the predictor of 10 or more inpatient days to age greater than 55 increased the likelihood of an OLA switch from 51 to 69%. Thus the effect of the substantial number of inpatient days at a certain point seems to overwhelm the effect of older age to reduce the likelihood of an OLA switch. This allows the potential identification of different "subgroups" with high likelihood of an OLA switch: one group of patients who were younger than 55 years and especially if they have one or more inpatient days and a second group patients who were older than 55 years but had 10 or more inpatient days. Thus the signal detection techniques, because they allow specific cut-points and the examination of interactions between variables with specific cut-points, may facilitate the identification of clinically relevant subgroups (see Fig. 2).

It should be emphasized that the signal detection techniques used in these analyses are exploratory techniques. However, with large data sets the sample may be split and one can perform both exploratory analyses on one portion of the data and confirmatory analyses on the second portion of the data. Furthermore, the confirmatory analyses could include targeted regression analyses for the interactions identified in the exploratory analyses. However, to perform such a two-stage analysis large sample sizes are required. The minimal size of data sets required for a signal detection analysis such as that performed in this article is probably on the order of 200 subjects. The confirmatory analyses, if they used regression techniques, would likely require fewer subjects.

Although we have applied signal detection techniques to a question that involves physician choice, there are many other applications of this type of analysis. In general, any outcome that can be coded as a binary or

yes/no decision can be the subject of a signal detection analysis. Prior work has included prognosis (Killen et al., 1996; O'Hara et al., 2002) and prediction of treatment response (Winkleby et al., 1994). Predictors of response also must be objective. This is particularly difficult in predicting physician prescribing practices, which may at times be based on unconscious decisions. This might be possible, for example, in situations where there was racial bias in prescribing and one knew the race of the patients. On the other hand, if there are other ethnic differences in the patient population that were not qualified and the prescriber was biased on the basis of those characteristics, the ROC could not perform an identification of such factors.

Another obstacle to the completion of such analyses in the past has been the lack of statistical software to compute the relevant signal detection measures—sensitivity and specificity—and complete the iterative process of selecting the best choice points. Some software is available in statistical packages to perform similar "recursive partitioning" techniques. Some of these techniques, however, are limited because the separation into subgroups is done without regard to the relative clinical importance of false positives and false negatives, i.e. based solely on χ^2 criteria. Often at one stage of the partitioning (because of the χ^2 criterion they use) one will be emphasizing sensitivity, while at another point in the analysis emphasizing specificity. The ROC software used in this analysis has the advantage that its decision criteria are based on sensitivity and specificity criteria that can be adjusted to equally balance sensitivity versus specificity, or favor one versus the other. For example, if one were testing a method to identify breast cancer, one might favor sensitivity of test, whereas if one were screening for a dangerous surgical procedure, one might favor specificity of test. Thus the ROC approach allows one to tailor the analysis to one's desire to emphasize sensitivity, specificity or equally weight them both.

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