Suicide Risk in Bipolar Disorder During Treatment With Lithium and Divalproex

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Objective To compare risk of suicide attempt and suicide death during treatment with lithium with that during treatment with divalproex.

Design and Setting Retrospective cohort study conducted at 2 large integrated health plans in California and Washington.

Patients Population-based sample of 20638 health plan members aged 14 years or older who had at least 1 outpatient diagnosis of bipolar disorder and at least 1 filled prescription for lithium, divalproex, or carbamazepine between January 1, 1994, and December 31, 2001. Follow-up for each individual began with first qualifying prescription and ended with death, disenrollment from the health plan, or end of the study period.

Main Outcome Measures Suicide attempt, recorded as a hospital discharge diagnosis or an emergency department diagnosis; suicide death, recorded on death certificate.

Results In both health plans, unadjusted rates were greater during treatment with divalproex than during treatment with lithium for emergency department suicide attempt (31.3 vs 10.8 per 1000 person-years; \( P < .001 \)), suicide attempt resulting in hospitalization (10.5 vs 4.2 per 1000 person-years; \( P < .001 \)), and suicide death (1.7 vs 0.7 per 1000 person-years; \( P = .04 \)). After adjustment for age, sex, health plan, year of diagnosis, comorbid medical and psychiatric conditions, and concomitant use of other psychotropic drugs, risk of suicide death was 2.7 times higher (95% confidence interval [CI], 1.1-6.3; \( P = .03 \)) during treatment with divalproex than during treatment with lithium. Corresponding hazard ratios for nonfatal attempts were 1.7 (95% CI, 1.2-2.3; \( P = .002 \)) for attempts resulting in hospitalization and 1.8 (95% CI, 1.4-2.2; \( P < .001 \)) for attempts diagnosed in the emergency department.

Conclusion Among patients treated for bipolar disorder, risk of suicide attempt and suicide death is lower during treatment with lithium than during treatment with divalproex.

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For editorial comment see p 1517.
maintenance treatment of bipolar disorder. Furthermore, substantial data have accumulated regarding the anti-suicide effects of lithium. In a recent meta-analysis of 33 studies (including primarily patients with bipolar disorder), Baldessarini et al20 found that the annual rate of attempted or completed suicide was 0.197% during lithium treatment compared with 2.57% without lithium, a 13-fold difference. In the United States, use of lithium has declined over the last decade while use of anticonvulsants (especially divalproex and several newer agents) for treatment of bipolar disorder has steadily increased. Divalproex generates at least 10 times more sales revenue than does lithium (Joanne Kearney, Solvay Pharmaceuticals, written communication based on IMS Health National Sales Perspectives audit for fiscal year 2002, August 15, 2003), so industry-supported education regarding divalproex far exceeds that for lithium.

Surprisingly few studies address the effect of anticonvulsant mood stabilizers on suicide risk. A single randomized trial by Thies-Flechtner et al21 compared maintenance treatment with lithium or carbamazepine in 175 patients with bipolar disorder discharged from psychiatric inpatient units. There were no suicide attempts or suicide deaths in the lithium group compared with 9 suicide events in the carbamazepine group, a significant difference at P = .01. No systematic data are available regarding suicide during treatment with divalproex, currently the most widely used mood stabilizer in the United States (Sandra Mertz, Abbott, oral communication based on IMS Health and Verispan/Scott-Levin data for July 2003, August 26, 2003).

This study examined the risk of attempted and completed suicide among patients treated for bipolar disorder in 2 large integrated health plans. Administrative databases were used to identify those treated for bipolar disorder, assess potential confounding factors, and ascertain periods of exposure to lithium, divalproex, and carbamazepine. Suicide attempts were identified using emergency department (ED) visit and hospital discharge diagnoses. Suicide deaths were identified using both health plan mortality records and relevant state death certificate records.

**METHODS**

**Study Settings**

Two managed care organizations participated in this study, Kaiser Permanente (KP) and Group Health Cooperative (GHC). Both plans provide comprehensive medical care, including mental health care. Kaiser Permanente serves an ethnically diverse population of more than 3 million persons, about 30% of the entire population in the San Francisco Bay Area, Sacramento, and nearby northern California counties. The group-model portion of GHC (in which this study was conducted) serves approximately 450,000 members in western Washington State. Most members of both plans are covered through employer-purchased plans, but approximately 15% are covered via contracts with Medicare, Medicaid, or other low-income programs. At KP, there are 16 large medical centers and 29 specialty mental health clinics. At GHC, there are 24 medical centers and 6 specialty mental health clinics. The clinics at both KP and GHC are staffed by psychiatrists, psychologists, licensed clinical social workers, psychiatric nurse practitioners, psychiatric nurses, and masters-level psychotherapists.

Kaiser Permanente members are generally similar to the non-KP population of northern California, although poor and elderly persons are somewhat underrepresented in KP. Group Health Cooperative members are comparable with Seattle-area residents except for a higher educational level and a lower percentage of high-income residents.22 The computerized information systems at KP and GHC include data on all hospital discharges, ED visits, outpatient clinic visits, and outpatient prescriptions filled in KP or GHC pharmacies. An estimated 96% of patients with bipolar disorder at KP had pharmacy benefits in 2001. Surveys of GHC members indicate that more than 95% of prescriptions filled by GHC members are obtained at GHC pharmacies.24,25

**Inclusion/Exclusion Criteria**

This retrospective cohort study included all members aged 14 years or older who had a record of outpatient treatment for bipolar disorder and were enrolled in KP or GHC at any time from January 1, 1994, to December 31, 2001 (Table 1). Institutional review boards at GHC and KP approved all study procedures. Specific inclusion criteria were (1) at least 1 outpatient diagnosis of bipolar disorder type 1 or type 2 on or after the 14th birthday (ie, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] diagnosis codes 296.4x, 296.5x, 296.6x, 296.7, 296.89, and 296.80) during the study period and (2) at least 1 prescription for lithium, divalproex, or carbamazepine filled at a KP or GHC pharmacy during the study period. Specific exclusion criteria were (1) diagnosis of schizophrenia (DSM-IV code 295.xx, except 295.7x) on more than 1 occasion at any time during the study period, (2) any diagnosis of schizoaffective disorder (DSM-IV code 295.7x) occurring before the first recorded diagnosis of bipolar disorder, or (3) any diagnosis of dementia or cognitive disorders occurring before the first recorded diagnosis of bipolar disorder.

Patients with a diagnosis of schizoaffective disorder occurring after the first bipolar disorder diagnosis were included but censored on the date of the first schizoaffective diagnosis. For each patient selected, the period of observation began with the first filled prescription for lithium, divalproex, or carbamazepine during the study period and ended with death, disenrollment from the health plan, or the end of the study period, December 31, 2001.

**Outcome Measures**

We identified 3 different classes of suicide-related events: suicide mortality, suicide attempts resulting in hospitalization, and suicide attempts or suicidal behavior resulting in ED visits but not hospital admissions.
Suicide mortality was identified using mortality files from state departments of health for the period January 1, 1994, through December 31, 2000. Suicide deaths were identified based on International Classification of Diseases, Ninth Revision (ICD-9) codes E950 to E959 for 1994 to 1998 and on International Classification of Diseases, Tenth Revision codes X60 to X84 and Y87.0 for 1999 and 2000. State mortality files were not yet available for 2001; consequently, the last year of the study period was included in analyses of suicide attempts but not deaths.

Suicide attempts were identified from computerized records of all ED visits or inpatient discharges with an ICD-9 diagnostic code in the range of E950 to E959 for the period January 1, 1994, to December 31, 2001. Specific checkboxes for “suicide gesture,” “suicide attempt,” and “suicidal behavior” were included on KP ED encounter forms for the entire study period. For most of the study period, GHC encounter forms included no such codes, so suicide attempt could only be recorded by handwritten diagnosis. Therefore, analyses of suicide attempts identified from ED visits included only KP patients. Suicide attempts identified from ED visits and those identified from inpatient stays were analyzed separately.

### Treatment Exposure

Treatment exposure was measured using computerized pharmacy records of all initial and refill prescriptions. For each prescription fill or refill, the period of exposure was considered to begin on the dispensing date and to continue for the expected duration of the prescription (ie, drug supply days) plus a grace period of either 14 days or 25% of the expected prescription duration (whichever was longer). Based on this rule, each day during the study period was classified by exposure to lithium, divalproex, carbamazepine, a combination of these mood stabilizers, or none of these 3 drugs. Depending on the pattern of medication switches, an individual patient might contribute follow-up time to any or all of these exposure groups. The combination period represented mostly combination therapy but also included exposure time during transition from one medication to another.

### Potential Confounding Factors

Outpatient diagnoses were used to identify the following specific comorbid conditions (present prior to first mood stabilizer prescription) that might either introduce bias by influencing choice of mood stabilizer or indicate differences in preexisting risk of suicide: seizure disorder, thyroid disorder, hepatic disorder, renal disease, pancreatitis or other pancreatic disorder, anxiety disorders (including panic disorder, agoraphobia, posttraumatic stress disorder, generalized anxiety disorder, social phobia, and anxiety disorder not specified), and substance abuse. Using the described methods for measurement of treatment exposure, pharmacy records were used to identify concomitant use of specific psychotropic drugs, including antidepressants, typical antipsychotics, and atypical antipsychotics.

### Statistical Analysis

Descriptive statistics and crude (unadjusted) rates of suicide mortality and suicide attempt are reported for periods of treatment with lithium, divalproex, or carbamazepine; combined treatment (lithium plus divalproex or carbamazepine); and no exposure to any of the 3 drugs. Rates are reported per 1000 person-years of treatment exposure. Our focus was on the comparison of lithium with divalproex or carbamazepine. It is difficult to interpret the experience of patients who are untreated or who receive combined treatment. We suspect that the former are a heterogeneous group including those with relatively mild disease and those with adherence problems and the latter are more likely to have severe or treatment-resistant disease.

Exact binomial tests were used to compare the unadjusted suicide rate during periods of lithium exposure with the suicide rate during periods of divalproex or carbamazepine exposure. For each type of suicide outcome, Cox proportional hazards regression models were
used to examine risk in relation to exposure to each type of mood stabilizer after adjustment for age, sex, health plan, year of diagnosis, comorbid medical and psychiatric conditions, and concomitant use of other psychotropic drugs. Periods of exposure to mood stabilizers and concomitant psychotropic drugs were analyzed as time-dependent variables. Thus, patients who switched from one mood stabilizer to another contributed information to estimates of the suicide risks associated with each of the drugs. Risk during treatment with lithium alone was the reference category for comparisons among mood stabilizers.

Risk sets were blocked by year of diagnosis and health plan. Because some patients attempted suicide more than once, analyses of attempts used the counting-process specification of the Cox model with robust variance estimation. Weighted Schoefeld residuals were examined to assess the proportional hazards assumption that the relative risks do not change over time. For all comparisons of divalproex vs lithium—regarding suicide attempts as well as deaths—the residuals were not significantly correlated with time (P > .10). For relative risk estimates, 95% confidence intervals (CIs) are reported. P < .05 indicates statistical significance for all analyses and SAS software was used for all analyses.

**RESULTS**

We identified 20638 health plan members treated for bipolar disorder during the study period (16 248 at KP and 4390 at GHC) who fit the study inclusion and exclusion criteria. Demo-

<table>
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<tr>
<th>Table 2. Numbers and Rates of Suicide Attempts and Suicides During Periods of Exposure to Each Mood-Stabilizing Drug</th>
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<tr>
<td><strong>Lithium Only</strong></td>
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<td><strong>Kaiser Permanente</strong></td>
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<td>Person-years of observation</td>
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<td>Suicide deaths</td>
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<td>Suicide attempts ascertained in emergency department</td>
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<td>Event rate per 1000 person-years</td>
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<td>Suicide attempts resulting in hospitalization</td>
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<td>Event rate per 1000 person-years</td>
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<td><strong>Group Health Cooperative</strong></td>
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*Risk during treatment with lithium alone is the reference category for comparisons among mood stabilizers.
graphic and clinical characteristics of the study sample at the 2 sites are shown in Table 1. At both sites, the treated bipolar population was predominantly female and younger than 45 years. At both sites, 70% of patients filled at least 1 prescription for an antidepressant drug. There were 53 suicides, 338 attempts resulting in hospitalization, and 642 attempts identified in the ED. Of the 53 suicide deaths, 16 (30%) were caused by guns, 14 (26%) by poisoning, 11 (21%) by hanging/suffocation, and 12 (23%) by other methods. Table 2 displays periods of exposure, number of suicide-related events, and rates of suicide-related events at both study sites. There was a total of 60060 person-years of observation (ie, a mean follow-up period of approximately 2.9 years per individual). There was no exposure to lithium, divalproex, or carbamazepine during nearly half (47%) of all person-years of follow-up. Patients were exposed to lithium alone during 27% of follow-up, divalproex alone during 18%, carbamazepine alone during 4%, and a combination of these mood stabilizers during the remaining 4%.

Suicide attempts resulting in hospitalization occurred 6.2 times more frequently than suicide deaths. At KP, suicide attempts ascertained in the ED occurred 14.6 times more frequently than ED suicide deaths. For each outcome examined at each site, rates of suicide attempt and suicide death were substantially greater during periods of exposure to divalproex than that of lithium (Table 2). During periods with no mood stabilizer exposure, 8 (32%) of the 25 suicide deaths occurred within 30 days of discontinuation of a mood stabilizer, whereas only 12% of the total follow-up time was within 30 days of discontinuation (P = .01).

After adjustment for age, sex, health plan, year of diagnosis, comorbid medical and psychiatric conditions, and concomitant psychotropic drug use, the risk of each of the 3 outcomes was significantly greater during exposure to divalproex than during exposure to lithium; hazard ratios were 2.7, 1.7, and 1.8 for suicide death, attempt resulting in hospitalization, and attempt ascertained in the ED, respectively (Table 3). In each of the plans, the risk of each of these 3 outcomes during exposure to divalproex was greater than during exposure to lithium. Differences between health plans regarding comparisons of divalproex vs lithium were not significant (for suicide death, P = .60; for attempt resulting in hospitalization, P = .37).

Table 3. Risk of Suicide Attempts and Death in Relation to Use of Divalproex or Carbamazepine vs Lithium*

<table>
<thead>
<tr>
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<th>Divalproex</th>
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<th>Carbamazepine</th>
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<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Suicide attempts ascertained in emergency department</td>
<td>1.8 (1.4-2.2)</td>
<td>&lt;.001</td>
<td>1.4 (1.0-2.0)</td>
<td>.09</td>
</tr>
<tr>
<td>Suicide attempts resulting in hospitalization</td>
<td>1.7 (1.2-2.3)</td>
<td>.002</td>
<td>2.9 (1.9-4.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Suicide deaths</td>
<td>2.7 (1.1-6.3)</td>
<td>.03</td>
<td>1.5 (0.3-7.0)</td>
<td>.61</td>
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</table>

Abbreviation: CI, confidence interval.
*Hazard ratios for divalproex and carbamazepine use calculated (with lithium use as referent) by Cox regression analysis adjusted for age, health plan, year of diagnosis, medical and psychiatric comorbidities, and concomitant psychotropic drugs.

Results for other comparisons (ie, lithium vs carbamazepine, lithium vs combination treatment, and lithium vs none of the mood stabilizers) were less consistent or stable. During periods of treatment with carbamazepine alone compared with lithium alone, the hazard ratios of the 3 outcomes ranged from 1.4 to 2.9, but only the hazard ratio of attempts resulting in hospitalization was significantly different from 1 (Table 3). During the 4% of follow-up time when patients were exposed to combination treatment, the risk of suicide attempt—ascertained in either the hospital or the ED —was similar to the risk with divalproex alone and more than twice as high as the risk of suicide attempt with lithium alone. Risk of suicide death was not significantly higher during combination therapy, but the 95% CI for the relative risk estimate of 2.1 was very wide (0.6-7.7). Compared with periods of treatment with only lithium, periods with no mood stabilizer treatment were associated with relative risks of 2.2, 1.6, and 1.4 for suicide death, suicide attempt ascertained in the ED, and suicide attempt resulting in hospitalization, respectively.

Additional secondary analyses examined the possibility that differences in suicide risk associated with exposure to different mood stabilizers could reflect differences in preexisting illness severity or other factors affecting suicide risk (ie, confounding by indication). First, we examined the hypothesis that the selection of one mood stabilizer rather than another was determined more by temporal trends in prescribing than by characteristics of individual patients. The Figure displays the distribution of first

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mood-stabilizing drugs prescribed according to year of initial diagnosis. The ratio of initial filled prescriptions for lithium to that for divalproex shifted from approximately 6:1 in 1994 to approximately 1:2 in 2001. This shift is consistent with shifts in prescribing behavior from lithium to divalproex during this time frame noted in other settings.30-32 We also examined whether risk differences between lithium and divalproex were stable throughout the study period. For suicide attempts, rates during lithium exposure were consistently lower than during anticonvulsant treatment throughout the 8-year period. For suicide deaths, the risk difference was less consistent over time and appeared smaller during the first half of the study period. Given the smaller number of suicide deaths, this trend may have been due to chance (P = .13). In addition, we evaluated the hypothesis that patients with higher suicide risk were more likely to be switched from one class of mood stabilizer to another by examining suicide risk in the subgroups of patients switching classes of mood stabilizers (from lithium to divalproex or the reverse) and the subgroups of patients continuing in the same class (lithium or divalproex). Among those exposed to divalproex, a previous switch from lithium was associated with a significantly higher risk of suicide attempt resulting in hospitalization (hazard ratio, 2.0; 95% CI, 1.1-3.4). But among those switching from divalproex to lithium, there was a similar increase in risk of suicide attempt resulting in hospitalization (hazard ratio, 1.8; 95% CI, 0.9-3.6). Therefore, a history of any medication switch was associated with a higher risk of suicide attempt, but this effect did not differ by direction of the switch (from lithium to divalproex vs the reverse).

COMMENT

In this population-based sample of more than 20000 persons treated for bipolar disorder, we found that risk of suicide attempt or suicide death was 1.5 to 3 times higher during periods of treatment with divalproex than during periods of treatment with lithium. This difference in risk was consistent across all outcome measures (suicide death, attempt resulting in hospitalization, and attempt diagnosed in the ED) and across the 2 study sites. Results for carbamazepine were qualitatively similar to those for divalproex but (reflecting the smaller sample size) much less precise. The findings reported here are consistent with substantial previous data suggesting that lithium reduces suicide attempts and suicide mortality.20 The current study complements a previous study33 comparing lithium and carbamazepine. Another small observational study34 found no difference in risk of suicidal behavior during treatment with lithium compared with treatment with divalproex or carbamazepine, but its sample size was not adequate to detect 2- or 3-fold differences in risk. To our knowledge, this is the first study comparing suicide deaths and attempts associated with lithium and divalproex, the most widely used mood stabilizer in the United States.

Several limitations are inherent in the use of administrative databases for this type of research. First, we relied on the treating clinician’s discharge or encounter diagnoses rather than structured research evaluations to identify patients treated for bipolar disorder. Second, we relied on diagnosis and prescription data rather than clinical assessments to adjust for differences in illness severity or underlying suicide risk. Third, visit or discharge diagnosis data may miss a significant proportion of true suicide attempts.

No observational study can completely exclude the possibility of confounding by indication or bias due to unmeasured differences in illness severity or suicide risk in those treated with lithium and those treated with divalproex or carbamazepine. Still, we made every attempt to detect and adjust for this bias in our analyses. First, we controlled for characteristics that might indicate greater severity of illness or suicide risk or might influence choice of mood stabilizer (eg, comorbid medical or psychiatric illness, concomitant use of other psychotropic drugs). Second, analyses of time trends in prescribing (Figure) suggest that choice of either lithium or an anticonvulsant was more strongly influenced by secular trends in prescribing than by clinical characteristics of individual patients. Despite dramatic changes in prescribing patterns over time, the lower risk during lithium treatment was consistent throughout the study period. Third, our analyses of those switching between mood stabilizers does not suggest that switching from lithium to divalproex was preferentially associated with higher suicide risk. Only a randomized trial can completely exclude the possibility of confounding or bias, but large observational studies such as this one may be the only realistic option for studying relatively rare outcomes such as suicide death.

Although our analyses support the validity of comparing lithium treatment with divalproex treatment, we urge caution in interpreting comparisons with combination treatment or periods with no mood stabilizer treatment. Decisions (by care providers or patients) to discontinue a mood stabilizer or to initiate combined treatment are almost certainly related to perceived severity of illness and anticipated risk of suicide attempt. Consequently, confounding by indication may seriously bias any comparison of risk during single-drug treatment (with lithium or divalproex) with that during either combined treatment or no treatment. Furthermore, the total exposure to combination treatment in this sample was too small to support accurate estimates of suicide risk. Given the importance of combination treatment for some patients, future research should evaluate whether the apparently lower suicide risk during lithium treatment also occurs during treatment with lithium-anticonvulsant combinations.

We included carbamazepine in these analyses to allow comparison with the only previous randomized comparison study of suicide risk during mood stabilizer treatment.21 Our findings are consistent with that study, although our power to evaluate carbamazepine is low because only 4% of follow-up was in patients treated with carbamazepine only.

The mechanism by which lithium might exert an antisuicide effect is not
clear. Several controlled studies have demonstrated modest efficacy of lithium in treatment and prevention of bipolar depression.34–38 Randomized trials have also demonstrated that lithium reduces aggressive behavior in prisoners39–41 and reduces impulsive behavior in children and adolescents.42–44 At the biological level, suicide death is clearly associated with reduced functional capacity of central serotonin systems.45 Long-term lithium administration enhances serotonin turnover, reflected by increased release and down-regulation of serotonin receptor sites in the rat hippocampus.46 This evidence of lower suicide risk during lithium treatment should be viewed in light of the declining use of lithium by psychiatrists in the United States, particularly among recently trained psychiatrists. Many psychiatrists have no or limited experience prescribing lithium, largely a reflection of the enormous focus on the newer drugs in educational programs supported by the pharmaceutical industry. If lithium does have an antidepressive effect not matched by currently available alternatives, then current prescribing patterns should be reevaluated. At the least, use of lithium to treat mood disorders should be an essential component of training in psychiatry.

Author Contributions: Dr Goodwin, as principal investigator, had full access to all of the data in this study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goodwin, Fireman, Simon, Hunkeler, Revicki. Acquisition of data: Fireman, Simon, Hunkeler, Lee. Analysis and interpretation of data: Goodwin, Fireman, Simon, Hunkeler, Lee, Revicki. Drafting of the manuscript: Goodwin, Fireman, Simon, Lee, Revicki. Critical revision of the manuscript for important intellectual content: Goodwin, Fireman, Simon, Hunkeler, Revicki. Statistical expertise: Fireman, Simon, Lee, Revicki. Obtained funding: Goodwin. Administrative, technical, or material support: Goodwin. Study supervision: Goodwin, Fireman, Hunkeler. Funding/Support: This study was supported by funding from Solvay Pharmaceuticals to Best Practice LLC based on a proposal developed by the study investigators.

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REFERENCES


