Benzodiazepine Prescription Practices and Substance Abuse in Persons With Severe Mental Illness

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Background: Benzodiazepines have many benefits for persons with severe mental disorders, but they may also lead to or exacerbate substance abuse. An American Psychiatric Association taskforce established practice guidelines in 1990 to assist physicians in managing these and other potential side effects of benzodiazepine use. The objectives of this study were to determine the prevalence of benzodiazepine use among persons with psychiatric disorders and to evaluate compliance with published prescribing guidelines.

Method: We studied benzodiazepine use among New Hampshire Medicaid beneficiaries aged 18 to 64 years with ICD-9 diagnoses that were grouped under the headings "schizophrenia," "bipolar disorder," "major depression," and "other psychiatric disorders" from Jan. 1995 through Dec. 1999. Rates and length of use, frequency of high-potency/fast-acting prescriptions, and diazepam-equivalent dosages were compared for those with and without retrospectively determined evidence of substance abuse, substance dependence, or a procedure code indicating treatment for a substance use disorder (SUD).

Results: Five-year prevalence of benzodiazepine use for persons with and without SUD was 63% versus 54% for schizophrenia, 75% versus 58% for bipolar disorder, 66% versus 49% for major depression, and 48% versus 40% for other psychiatric disorders. Differences were statistically significant over 5 years and in 1999 ($p < .0001$). Among persons with major depression or other psychiatric disorders, those with comorbid SUD were more likely to use fast-acting/high-potency benzodiazepines; there were no such differences for those with schizophrenia or bipolar disorder. Persons with bipolar disorder or other psychiatric disorders and SUD received significantly higher diazepam-equivalent dosages than did those without SUD.

Conclusion: Contrary to published guidelines, rates of benzodiazepine use are higher among Medicaid beneficiaries with severe mental illness and co-occurring SUD than among persons with severe mental illness alone. Additional research and possibly a reassessment of prescribing guidelines are recommended.

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Benzodiazepines, such as alprazolam, lorazepam, and clonazepam, are often prescribed for persons with a severe mental illness such as schizophrenia, bipolar disorder, or major depression. These medications can reduce anxiety, agitation, and sleeplessness; relieve side-effects of traditional antipsychotics such as haloperidol; or augment antimanic agents in treating mania or antipsychotics in treating persistent psychosis.[1–3] In addition to its benefits, benzodiazepine use can lead to abuse of benzodiazepines or other substances.[4,5] High rates of benzodiazepine prescription, coupled with an elevated risk of substance abuse, may place persons with severe mental illness at greater health risk than other diagnostic groups. For example, a recent prospective study of persons with schizophrenia and substance use disorders (SUD) found that benzodiazepine treatment did not improve outcomes, and persons who were prescribed benzodiazepines were more likely to abuse them.[6]

Benzodiazepines can interact with alcohol and other substances of abuse to increase or modulate symptoms of intoxication, and users can become addicted to the medications themselves. In 1990, an American Psychiatric Association panel on benzodiazepine dependency recommended that physicians use the medications for brief treatment but concluded that "Risks of chronic toxicity, especially cognitive impairment, true physiological dependence, and discontinuance symptoms, are all more likely under the following conditions: (1) high dose, (2) daily dosing of more than 4 months duration, (3) advanced age, (4) current or prior history of sedative hypnotic and/or alcohol dependence, and use of high-potency, short half-life benzodiazepines" (p. 59).[7] At present, we know relatively little about the extent to which these precautions are followed for persons with severe mental illness.

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Patients with disability due to schizophrenia, bipolar disorder, or major depression may, for the therapeutic reasons outlined above, be more likely to receive benzodiazepines and therefore face greater risks from them than would persons with less severe disorders. Epidemiological evidence suggests that persons with these disorders have higher lifetime rates of SUD than do other groups.[8] Clinical characteristics, prescribing practices, and greater susceptibility to substance abuse could combine to place persons with severe mental illness at greater risk for problems associated with benzodiazepine use.

We use data from New Hampshire Medicaid beneficiaries to study benzodiazepine prescriptions for persons with schizophrenia (including schizoaffective disorder), bipolar disorder, major depression, and other psychiatric disorders. The objectives of this study were to determine the prevalence of benzodiazepine use among persons with psychiatric disorders and to evaluate compliance with published prescribing guidelines. Specifically, we focus on the following questions: How many persons with severe mental illness are prescribed benzodiazepines? Are persons with comorbid severe mental illness and SUD prescribed benzodiazepines less frequently and/or for shorter durations than are persons with severe mental illness alone? Are persons with co-occurring disorders less likely than persons with severe mental illness alone to be prescribed benzodiazepines thought to have higher addiction potential, and do they receive lower dosages?

METHOD

In a retrospective analysis, we used all paid Medicaid claims for New Hampshire Medicaid beneficiaries 18 to 64 years of age between 1995 and 1999 to identify those beneficiaries with any type of psychiatric disorder and, among those, persons who also had a SUD. For persons with both Medicaid and Medicare eligibility, Medicare claims were also used to identify psychiatric disorders and SUDs. Persons eligible for only Medicare were not included in the study because their pharmaceutical claims were unavailable. Those with diagnoses of Alzheimer's disease, other dementia, or mental retardation were excluded from the analysis group. Persons with primary ICD-9 diagnoses were combined into the following groups for this analysis: "schizophrenia" (295.00–295.95), "bipolar disorder" (296.00–296.09, 296.40, 296.50, 296.60, 296.70, 296.89), or "major depression" (296.20–296.36). Other psychiatric disorders were grouped into a single category. Those with any diagnosis of substance abuse or dependence (alcohol or other drug, excluding tobacco), or who received treatment under a procedure code specifically designated for substance abuse treatment were identified as having a SUD during the year in which the indicator was observed.

Study Population

For purposes of comparing rates of benzodiazepine use, we used all Medicaid beneficiaries aged 18 through 64 years who received treatment for a primary psychiatric disorder of any kind, other than solely a SUD, during the 5-year study period (N = 10,003). Mean age was 37.4 years (SD = 11.5) and 2832 (28.3%) of the subjects were women. More than a quarter (27.4%) of the Medicaid beneficiaries also received Medicare benefits for at least 1 month during the study period, with approximately one fifth (19.3%) receiving benefits for the entire period. Of the 10,003 beneficiaries selected in the original sample, 9589 were continuously eligible over the 5-year period; those without continuous eligibility were dropped from the 5-year sample. In 1999, 9881 persons were eligible.

Of 1705 people who received treatment for schizophrenia in December of 1999, 93.4% used antipsychotic medication; 42.5% used a traditional antipsychotic such as haloperidol or chlorpromazine, 43.1% used olanzapine, 21.5% used clozapine, 22.5% used risperidone, and 13.8% used quetiapine; one half (51.4%) used an antidepressant.

Among persons with bipolar disorder (N = 783), 379 (48.4%) used antipsychotics; 137 (17.5%) used a traditional antipsychotic, 177 (22.6%) used olanzapine, 106 (13.5%) used risperidone, 81 (10.3%) used quetiapine, and fewer than 10 used clozapine; three quarters (74.4%) used an antidepressant.

A smaller percentage of beneficiaries with major depression (N = 4182) used antipsychotics (N = 648; 15.5%). Percentages were fairly evenly distributed across traditional antipsychotics (4.4%), olanzapine (6.3%), risperidone (5.4%), and quetiapine (3.7%). Most (80.5%) people used an antidepressant. Of these, 45.7% used a selective serotonin reuptake inhibitor, 47.4% used traditional antidepressants (tricyclics and monoamine oxidase inhibitors), and 28.5% used other novel antidepressants.

Among people with other psychiatric disorders (N = 3211), 11% used antipsychotic medications. Percentages were evenly distributed among traditional antipsychotics (3.5%), olanzapine (4.6%), risperidone (3.2%), and quetiapine (2.2%). Slightly less than one half (48.1%) used antidepressants. Of these, 29.0% used traditional, 21.3% used SSRIs, and 13.6% used other novel agents.

Analysis

We compared rates of outpatient benzodiazepine use among persons with schizophrenia, bipolar disorder, major depression, and other psychiatric disorders and between persons in these groups with and without comorbid SUD using simple nonparametric statistics.

To assess whether persons with SUD were prescribed lower-risk benzodiazepines according to recommendations, we evaluated duration of medication use as

Table 1. Prevalence of Benzodiazepine Use in Patients With Severe Mental Illness With and Without Substance Abuse

	1995–1999[a]								1999[b]							
Substance	Schizophrenia (N = 1552)		Bipolar Disorder (N = 491)		Major Depression (N = 3757)		Other Psychiatric Disorders (N = 3789)		Schizophrenia (N = 1705)		Bipolar Disorder (N = 783)		Major Depression (N = 4182)		Other Psychiatric Disorders (N = 3211)	
Abuse Status	N/N	%	N/N	%	N/N	%	N/N	%	N/N	%	N/N	%	N/N	%	N/N	%
Alcohol (only)	29/57	50.88	16/26	61.54	98/154	63.64	97/258	37.60	20/47	42.55	N/A[c]	50.00	43/72	59.72	24/55	43.64
Drug (only)	264/416	63.46	92/124	74.19	506/787	64.29	453/957	47.34	66/149	44.30	27/50	54.00	104/175	59.43	63/148	42.57
Any substance abuse[d]	384/614	62.54	170/228	74.56	785/1195	65.69	720/1496	48.13	100/228	43.86	44/81	54.32	175/286	61.19	94/220	42.73
No substance abuse	504/938	53.73	153/263	58.17	1243/2562	48.52	923/2293	40.25	591/1477	40.01	348/682	51.03	1586/3896	40.71	1014/2991	33.90

[a]N = 9589 for those continuously enrolled from 1995–1999.
[b]N = 9881 for those enrolled in 1999.
[c]Cell size smaller than 11; Centers for Medicare and Medicaid Services rules prevent presentation of Ns.
[d]Includes some persons who had both alcohol and drug use disorders.

well as use of "fast-acting/high-potency" benzodiazepines. Analysis of benzodiazepine use duration was restricted to persons with continuous Medicaid eligibility who used a benzodiazepine at least once. Fast-acting/high-potency benzodiazepines were defined as alprazolam, estazolam, and triazolam.[9]

All outpatient benzodiazepine prescriptions during December 1999 were combined by using a conversion table developed by Arana and Rosenbaum[9] to create a measure of diazepam-equivalent dosages for the final month of the study.

This analysis is part of a larger study of treatment for dual disorders, which was approved by Institutional Review Boards at the New Hampshire Department of Health and Human Services and Dartmouth Medical School.

RESULTS

Persons with schizophrenia, bipolar disorder, or major depression were more likely to use benzodiazepines than were persons with other psychiatric disorders. Among all diagnostic groups, those with comorbid SUD were more likely to use benzodiazepines than were those without substance use diagnoses. Between 1995 and 1999, rates of benzodiazepine use among persons with SUD were higher than 6 in 10 persons with schizophrenia or major depression and 7 in 10 persons with bipolar disorder (Table 1). Approximately 5 in 10 persons with other psychiatric disorders and substance use diagnoses used the medications. Differences were statistically significant across all groups ($\chi^2 = 16.58$, df = 1, $p < .0001$). A similar association between SUD and higher rates of benzodiazepine use can be seen in 1999 ($\chi^2 = 87.26$, df = 1, $p < .0001$).

Length of benzodiazepine use in 1999 varied by psychiatric diagnosis. A slightly lower percentage of substance abusers with schizophrenia used benzodiazepines for 4 months or more, and higher percentages of those with bipolar disorder, major depression, or other disorders used benzodiazepines for longer periods. Among substance abusers, 68.00% with schizophrenia, 81.81% with bipolar disorder, 64.57% with major depression, and 64.89% with other psychiatric disorders used benzodiazepines for 4 or more months. Percentages for persons without a substance use diagnosis were 71.24% for schizophrenia, 66.67% for bipolar disorder, 56.43% for major depression, and 52.47% for other psychiatric disorders ($\chi^2 = 41.55$, df = 1, $p < .0001$). Persons with major depression (25.17% vs. 14.6%; $\chi^2 = 22.94$, df = 1, $p < .0001$) or other psychiatric disorders (18.18% vs. 13.47%; $\chi^2 = 3.81$, df = 1, $p = .05$) and comorbid substance abuse were significantly more likely to use fast-acting/high-potency medications than were those without SUD. Differences between substance abusers and nonabusers with schizophrenia (5.26% vs. 4.27%; $\chi^2 = 0.47$, df = 1, $p = .49$) or bipolar disorder (18.52% vs. 13.49%; $\chi^2 = 1.52$, df = 1, $p = .22$) were not significant.

Mean diazepam-equivalent dosages were nominally higher but not significantly different for persons with schizophrenia with and without SUD (28.84 mg vs. 25.10 mg, df = 404, $p = .24$) or major depression (39.09 mg vs. 32.61 mg, df = 872, $p = .08$). Beneficiaries with bipolar disorder and SUD or other psychiatric disorders and SUD were prescribed significantly higher dosages than were their counterparts without SUD (49.71 mg vs. 36.20 mg, df = 219, $p = .05$ and 37.00 mg vs. 30.50 mg, df = 2006, $p = .02$).

DISCUSSION

In this study of adult New Hampshire Medicaid beneficiaries with severe mental illness we found high rates of benzodiazepine prescription and even higher rates for persons with comorbid SUD. Duration of use exceeded recommendations but was similar for those with and without SUD. Persons with major depression or other psychiatric

disorders and co-occurring SUD were more likely to use fast-acting/high-potency medications than were persons without comorbidity. Among persons with schizophrenia or bipolar disorder, there were no SUD-related differences in use of fast-acting/high-potency benzodiazepines. Diazepam-equivalent dosages were significantly higher for persons with co-occurring SUD among those with bipolar disorder or other less severe psychiatric disorders than for those without substance use diagnoses.

Persons with severe mental illness, who are more likely than those with other mental illnesses to develop SUD,[8] were more likely receive and to fill benzodiazepine prescriptions than were those with less severe diagnoses. Though American Psychiatric Association guidelines recommend caution when prescribing benzodiazepines to persons with SUD, prescribing physicians provided more benzodiazepines in the same or higher doses to persons with severe mental illness and SUD than to those without comorbidity. Frequency of prescribing fast-acting/high-potency benzodiazepines to persons with SUD was also similar to or higher than that for persons without comorbidity, and those with SUD tended to receive higher diazepam-equivalent dosages than did others.

It is not clear whether receiving benzodiazepine prescriptions increases the risk for developing a SUD or, conversely, that the presence of a SUD and other comorbidities that might be associated with it leads to anxiety or other symptoms appropriate for benzodiazepine treatment and to medication seeking, resulting in more prescriptions. Regardless of the causal direction, these data suggest that prescribers and policy makers across the country should reassess prescribing practices for persons with SUD co-occurring with psychiatric disorders.

There are some important caveats to these findings. Identification of SUD with insurance claims is imperfect and probably represents only those persons with the most severe substance abuse problems. Reasons for the suspected downward bias include the general tendency of practitioners to underdiagnose substance abuse in persons with severe mental illness[10] and the influence of payment incentives. Substance abuse treatment is reimbursed at lower levels than are similar mental health treatment services, and New Hampshire has limited Medicaid coverage for substance abuse treatment. Reimbursement policies may lead clinicians to define ambiguous cases as psychiatric rather than substance abuse related. This practice diminishes the chances that a substance abuse diagnosis will appear on the Medicaid claim. Thus, claims data may underestimate the true extent of substance abuse and, by extension, rates of benzodiazepine prescription for persons with comorbid disorders. Findings could differ in states with more comprehensive substance abuse treatment coverage and/or more favorable reimbursement rates.

Benzodiazepines are often used in alcohol or drug detoxification. Such use might account for some of the difference observed between those with and those without SUD. However, our analysis excludes medications used in inpatient settings and there were no outpatient detoxification programs in New Hampshire at the time of this study. Further, detoxification use alone is inconsistent with the lengths of use observed for most participants.

Benzodiazepine use was defined as prescriptions filled, which may not always correspond to actual usage. Although Medicaid prescriptions are routinely limited to a 1-month supply, patients could continue to use pills from a previous month, use benzodiazepines obtained illegally, or fail to use filled prescriptions at all. The extent of these potential problems is difficult to assess in this sample.

Minimal or no cost sharing by Medicaid beneficiaries is another feature of the study sample that may make them different from those with other types of health insurance. Nationwide, Medicaid beneficiaries with disabilities bear little or no cost for their prescriptions. Some states require a small copayment for brand name medications. Beneficiaries of other insurance plans, such as those offered by private companies or Medicare, are likely to face substantially higher out-of-pocket costs and, consequently, may be less likely to use benzodiazepines and other medications. Pharmacy benefits management, which restricts access to some medications and is used increasingly by states to manage Medicaid pharmaceutical costs, may also affect generalizability across states.

Limitations notwithstanding, this is the largest study of benzodiazepine use among persons with severe mental illness and comorbid substance abuse that we are aware of. Because the study includes an entire state population of Medicaid beneficiaries, rates of benzodiazepine prescription are relatively free from selection bias.

CONCLUSION

Rates of benzodiazepine prescriptions among people with severe mental illness are high and even higher for those with comorbid SUD. More careful monitoring of benzodiazepine prescriptions for this population seems appropriate. However, the added risk of causing or worsening a SUD must be balanced with the need for safe and effective treatments for anxiety, other psychiatric conditions, and medication side effects. It would be a mistake to adopt overly restrictive prescription policies.

Although benzodiazepines have been available for more than 40 years, there is still a great deal that we do not know about how they are used and how they affect treatment outcomes. Further research is needed to determine whether current guidelines regarding benzodiazepine prescription in persons with SUD are appropriate, and how prescriptions of such widely used drugs can be monitored without imposing undue burden on patients or physicians. More effective use of benzodiazepines is

likely to have substantial benefits for patients, especially those with schizophrenia and related disorders, and could lower the long-term costs of treatment.

Drug names: alprazolam (Xanax and others), chlorpromazine (Thorazine, Sonazine, and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), diazepam (Valium and others), estazolam (ProSom and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), triazolam (Halcion and others).

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