How Dosing of Ziprasidone in a State Hospital System Differs From Product Labeling

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Background: The purpose of this article is to review the utilization and dosing of ziprasidone in a state hospital system and to compare the dosing to dosing recommendations contained in product labeling that suggest a starting dose of 40 mg/day and a target dose range of 40 to 160 mg/day for schizophrenia.

Method: Dosing of ziprasidone was examined from the time when it was first marketed in 2001 up to and including calendar year 2006 using a database that contains patient information and drug prescription information for every inpatient within the adult civil facilities of the New York State psychiatric hospital system operated by the New York State Office of Mental Health. Supporting evidence for a therapeutic dose response for ziprasidone was examined by conducting a PubMed search for the period January 1, 1990, to June 1, 2008, identifying English-language articles related to ziprasidone dose in schizophrenia using the search terms ziprasidone, dose, and schizophrenia.

Results: Although the highest efficacious dose of ziprasidone recommended in the manufacturer's product label is 160 mg/day, the mean dose of ziprasidone prescribed among patients hospitalized in New York State in calendar year 2006 and receiving antipsychotic medication (N = 7154) was 179 mg/day (N = 709), with 51.6% receiving doses in excess of 160 mg/day (N = 366). Patients discharged on treatment with ziprasidone (N = 189) received a mean dose of 206 mg/day. Patients with schizophrenia with a history of prior state hospital admission were more likely to receive doses greater than 160 mg/day. Clinicians in hospitals with the highest prescribing rates for ziprasidone were more likely to prescribe ziprasidone in excess of 160 mg/day. The initial dose on the first day for new starts on treatment with ziprasidone was 91 mg/day (N = 112). Published anecdotal reports describe the use of ziprasidone in excess of 160 mg/day and up to 640 mg/day among patients not responding to lower doses, but, currently, there are no published reports from double-blind randomized clinical trials establishing the utility of this high-dose treatment strategy.

Conclusions: Dosing of ziprasidone in a large state hospital system is higher than what has been established in the registration program for schizophrenia. Although there is anecdotal evidence describing the use of ziprasidone in excess of 160 mg/day, controlled clinical trials are needed to determine if these higher doses are more effective.

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Dosing of second-generation antipsychotics in clinical practice in state hospitals can differ substantially from dosing as outlined in the product labeling approved by the U.S. Food and Drug Administration.[1–3] This difference may exist because dosing established in premarketing pivotal studies does not necessarily reflect the clinical realities when treating patients who are commonly found in public psychiatric settings. Registration studies may be designed without the benefit of complete knowledge of dose-response relationships and implemented in study subjects who may differ from the patients who will generally receive these medications in the "real world." Examples of these differences include disease severity, chronicity, and the presence of comorbid psychiatric and medical conditions. Moreover, study design for registration protocols may err on the side of caution when selecting doses or the timing of titration to maximum dose, with the unintentional consequence of sacrificing efficacy.[4]

Ziprasidone is a second-generation antipsychotic that has demonstrated clinical efficacy for the treatment of schizophrenia and bipolar disorder; however, there is much uncertainty as to its optimal dose. The product label[5] states that efficacy in schizophrenia was demonstrated in a dose range of 40 to 200 mg/day, administered b.i.d. in short-term clinical trials, and that there were inconsistent trends toward dose response within the range of 40 to 160 mg/day. According to the label, an increase to a dose greater than 160 mg/day is not generally recommended, and "no additional benefit" was evidenced for doses above 40 mg/day

for the maintenance treatment of schizophrenia. In a prior study,[3] we found that a substantial number of inpatients with psychosis within the New York State psychiatric hospital system receive quetiapine in doses that are greater than what is recommended in the product labeling approved by drug regulatory agencies. This finding raises the question of whether or not the same could be found for other new antipsychotics. In the current study, we review the utilization and dosing patterns for ziprasidone in New York State in 2006 and the published evidence regarding whether or not higher doses of ziprasidone are more efficacious than lower doses.

METHOD

Data on antipsychotic utilization and dosing in the 17 adult civil facilities of the New York State psychiatric hospital system operated by the New York State Office of Mental Health (16 facilities as of April 1, 2006) were collected using the Integrated Research Database (IRDB) created by the Information Sciences Division of the Nathan S. Kline Institute for Psychiatric Research. The IRDB contains patient information (demographic characteristics, dates of admission/transfer/discharge, and diagnosis) and drug prescription information for every inpatient. This hospital system provides intermediate and long-term care for patients with severe and persistent mental disorders. Patients are virtually all admitted as transfers from community and municipal hospitals where they were receiving short-term care and found to be in need of a more extended hospitalization. The IRDB has been used to describe antipsychotic utilization and dosing,[1–3,6,7] co-prescribing of antipsychotics with mood stabilizers,[8–10] antipsychotic polypharmacy,[11] risk of new-onset diabetes mellitus,[12] the epidemiology of diabetes mellitus,[13] and effectiveness of antipsychotics.[14,15]

The utilization of ziprasidone is described in terms of demographic and clinical characteristics of the patients receiving ziprasidone as well as the dosing patterns of ziprasidone. Comparisons are made between the dosing of ziprasidone observed and the recommendations for the treatment of schizophrenia contained in the manufacturer's product label as approved by the U.S. Food and Drug Administration.[5] From the IRDB, each patient's daily dose of ziprasidone is averaged over the number of days ziprasidone was received by the patient during the reporting period (i.e., calculated by summing the daily dose for each day for each patient and dividing by the number of all medication days during the reporting period, producing a mean daily patient dose weighted by days). Quarterly dosing data are available from 2001 through 2006. Annualized dosing data are available for calendar years 2004 to 2006. Specific clinical characteristics reported include diagnosis (percentage of patients with schizophrenia or schizoaffective disorder), length of stay (percentage of patients with stays > 360 days), history of prior state hospitalization (percentage of patients with prior hospitalization), and co-prescription on a single day with other antipsychotics (percentage of patients co-prescribed) and anticonvulsants or lithium (percentage of patients co-prescribed).

Because the product label does not recommend dosing of ziprasidone in excess of 160 mg/day, we examined possible differences among patients receiving daily doses of 160 mg or less versus those receiving greater than 160 mg/day and the variation of rates of high dosing by individual facility. Patients discharged on treatment with ziprasidone were grouped separately regarding dosing and co-prescribing because patients discharged on treatment with ziprasidone represent persons who presumably experienced a positive therapeutic outcome. New ziprasidone prescriptions, antecedent antipsychotic, and initial dose for new starts on treatment with ziprasidone are also examined. For comparison, similar data on utilization and dosing trends regarding quetiapine are reported from the same database.[2,3]

A PubMed search for the period January 1, 1990, to June 1, 2008, was conducted to identify English-language articles related to ziprasidone dose in schizophrenia. Search terms used were ziprasidone, dose, and schizophrenia. Additional sources were obtained from the reference lists in the identified articles. Specific attention was paid to fixed-dose studies. A query was made to Pfizer, Inc., Medical Resources, New York, N.Y., on May 31, 2008 for any extant information regarding dose response and optimal dose for ziprasidone, as well as dosing of ziprasidone over 160 mg/day.

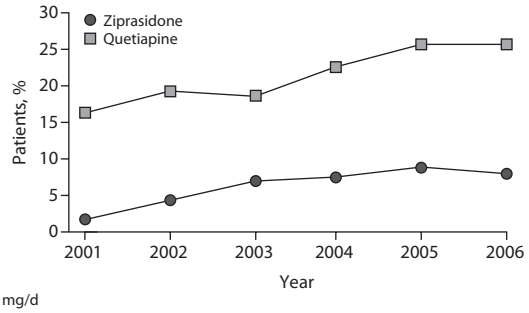
RESULTS

Utilization and mean daily dose of ziprasidone among inpatients receiving antipsychotics from 2001 through 2006 in the second quarter (from April 1 to June 30) of each year is displayed in Figure 1 together with that for quetiapine as a comparison. Table 1 describes the characteristics of the adult inpatient population in nonforensic hospitals receiving any antipsychotic medications by calendar year from 2004 through 2006. Table 2 describes the characteristics for those patients receiving ziprasidone.

During the reporting period of calendar year 2006, the number of patients receiving antipsychotic medication totaled 7154. Of these, 709 (9.9%) were receiving ziprasidone at a weighted mean (SD) dose of 179 (78) mg/day. Mean daily dose increased from 105 mg and 120 mg in the second quarters of calendar years 2001 and 2002, respectively, to 189 mg for the second quarter of 2006 (Figure 1).

Figure 2 describes the percentage of patients taking ziprasidone who received greater than 160 mg/day from 2001 to 2006 in the second quarter of each year. The proportion receiving doses in excess of 160 mg/day increased from 4.1% and 11.0% in the second quarters of 2001 and 2002, respectively,[2] to 47.9% for the second quarter of 2006 and

Figure 1. Patients in New York State Psychiatric Hospitals Who Received Ziprasidone or Quetiapine as a Percentage of Patients Receiving Any Antipsychotic Medication, 2001 to 2006, and Mean Daily Dose[a]



Mean dose, mg/d	2001	2002	2003	2004	2005	2006
Ziprasidone	105	120	135	145	168	189
Quetiapine	519	569	598	620	669	713

[a]Data was extracted from April 1 to June 30 for each calendar year. See also Citrome et al.[2]

Table 1. Characteristics of the Adult Inpatient Population Receiving Any Antipsychotic Medications: 2004 to 2006[a]

Variable	2004	2005	2006
Total, N[b]	7792	7595	7525
Prescribed antipsychotic	7289 (94)	7202 (95)	7154 (95)
Male[c]	4814 (66)	4761 (66)	4716 (66)
Nonwhite[c]	3968 (55)	3907 (54)	3870 (54)
Age, mean (SD), y[c]	43.9 (13.5)	44.3 (13.6)	44.4 (13.6)
Length of stay > 360 days[c]	3154 (43)	3128 (43)	2992 (42)
Schizophrenia or schizoaffective diagnosis[c]	5645 (78)	5599 (78)	5470 (76)
Prior state admission[c]	4776 (66)	4792 (66)	4736 (66)
Discharged in calendar year[c]	3384 (46)	3297 (46)	3254 (45)

[a]Values expressed as N (%) unless otherwise noted.
[b]In a total of 17 facilities until March 31, 2006, then 16 facilities.
[c]Among patients receiving antipsychotics.

to 51.6% for the entire calendar year of 2006. For comparison, the utilization of quetiapine at doses that exceed 750 mg/day is also displayed, a dose threshold selected because of the absence of efficacy data from controlled clinical trials for quetiapine dosing in excess of 750 mg/day (but note that the target dose range for quetiapine in product labeling is 300 to 500 mg/day).[3]

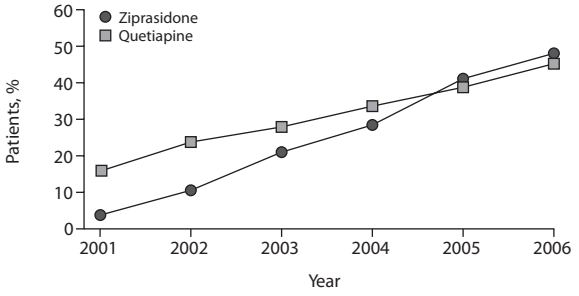
Table 3 describes the percentage of patients receiving ziprasidone in 3 dose ranges: less than or equal to 160 mg/day, greater than 160 to 200 mg/day, and greater than 200 mg/day. According to the product label, the highest recommended dose for efficacy is 160 mg/day, but safety data are available for doses up to 200 mg/day. Comparing patients receiving lower and higher doses of ziprasidone reveals only minor differences, but patients having a history of prior state hospital admission and those with schizophrenia were more likely to receive doses greater than 160 mg/day. Patients discharged on ziprasidone (N = 189), which can be interpreted as a successful therapeutic outcome, received a mean dose of 206 mg/day.

Table 2. Characteristics of the Adult Inpatient Population Receiving Ziprasidone: 2004 to 2006[a]

Variable	2004	2005	2006
Prescribed antipsychotic, N	7289	7202	7154
Prescribed oral ziprasidone among all patients receiving antipsychotics	721 (9.9)	821 (11.4)	709 (9.9)
Male[b]	411 (57.0)	495 (60.3)	419 (59.1)
Nonwhite[b]	372 (51.6)	400 (48.7)	349 (49.2)
Age, mean (SD), y	42.1 (12.8)	41.9 (13.2)	41.8 (13.4)
Length of stay > 360 days[b,c]	314 (43.8)	322 (39.2)	280 (39.5)
Schizophrenia or schizoaffective diagnosis[b]	578 (80.2)	643 (78.3)	541 (76.3)
Prior state admission[b]	488 (67.7)	568 (69.2)	467 (65.9)
Discharged in calendar year[b]	292 (40.5)	361 (44.0)	307 (43.3)
Admissions receiving antipsychotics, N	3349	3375	3381
Prescribed ziprasidone at some time during stay[d]	342 (10.2)	430 (12.7)	361 (10.7)
Prescribed ziprasidone on the day of admission[d]	207 (6.2)	284 (8.4)	249 (7.4)
Newly started on treatment with ziprasidone after the day of admission[d]	135 (4.0)	146 (4.3)	112 (3.3)

[a]Values expressed as N (%) unless otherwise noted.
[b]Among all patients receiving ziprasidone in the calendar year.
[c]Length of stay calculated from date of admission to discharge or end of calendar year, whichever comes first.
[d]Among all new admissions receiving antipsychotics.

Figure 2. Patients in New York State Psychiatric Hospitals Who Received Ziprasidone > 160 mg/day or Quetiapine > 750 mg/Day as a Percentage of Patients Receiving Any Dose of Ziprasidone or Quetiapine, Respectively, 2001 to 2006[a]



[a]Data was extracted from April 1 to June 30 for each calendar year. See also Citrome et al.[2]

Dosing of ziprasidone among patients receiving multiple psychotropic medications was also examined. Among discharged patients, receiving lithium, anticonvulsants, or other antipsychotics did not predict receiving lower doses of ziprasidone (Table 3). Among all patients receiving ziprasidone at one point in time (June 15, 2006), antipsychotic polypharmacy with ziprasidone was 56.8% for those receiving ziprasidone at doses less than or equal to 160 mg/day and 58.7% for those receiving ziprasidone in excess of 160 mg/day (Table 4). Results were comparable when this analysis was repeated for calendar days March 15, 2006; September 15, 2006; and December 15, 2006.

Table 3. Characteristics of the Adult Inpatient Population Receiving Ziprasidone During 2006 by Dose Range

Variable	N	Dose, Weighted Mean (SD), mg/d	Patients in Dose Range, %			Relative Risk (95% CI) for Receiving Dose >160 mg/d
			≤160 mg/d	>160 to 200 mg/d	>200 mg/d	
Total	709	179 (78)	48.4	20.6	31.0	NA
Gender						
Male	419	177 (78)	48.7	21.0	30.3	Male vs female: 0.99 (0.85 to 1.14)
Female	290	182 (79)	47.9	20.0	32.1	
Ethnicity						
White	360	186 (89)	46.9	18.9	34.2	Nonwhite vs white: 1.06 (0.92 to 1.22)
Black	245	171 (68)	50.6	22.4	26.9	
Hispanic	79	177 (58)	44.3	20.3	35.4	
Other	25	155 (58)	60.0	28.0	12.0	
Length of stay						
<30 d	52	188 (67)	44.2	7.7	48.1	≤360 d vs >360 d: 1.03 (0.89 to 1.19)
30–90 d	126	192 (91)	49.2	21.4	29.4	
91–180 d	126	171 (80)	55.6	17.5	27.0	
181–360 d	125	183 (76)	44.0	26.4	29.6	
361 d–5 y	184	176 (71)	45.7	21.2	33.2	
>5 y	96	168 (78)	51.0	21.9	27.1	
Prior state admission						
Yes	467	186 (80)	45.4	19.7	34.9	Prior history vs none: 1.19 (1.01 to 1.40)
No	242	166 (74)	54.1	22.3	23.6	
Diagnosis						
Schizophrenia	281	181 (71)	42.7	20.3	37.0	Schizophrenia vs nonschizophrenia: 1.20 (1.04 to 1.38)
Schizoaffective	260	181 (85)	49.2	21.5	29.2	
Bipolar	89	170 (73)	58.4	16.9	24.7	
Other	79	172 (86)	54.4	22.8	22.8	
Discharged patients[a]						
Receiving lithium or anticonvulsants	101	212 (99)	55.4	9.9	34.7	Receiving lithium or anticonvulsants vs not: 0.96 (0.70 to 1.31)
Not receiving lithium or anticonvulsants	88	200 (94)	53.4	8.0	38.6	
Discharged patients						
Receiving another antipsychotic	106	202 (88)	54.7	6.6	38.7	Receiving another antipsychotic vs not: 0.99 (0.72 to 1.35)
Not receiving another antipsychotic	83	212 (108)	54.2	12.0	33.7	

[a]Categorized by medication on day of discharge, one of which must be ziprasidone; dose of ziprasidone is dose on day of discharge.
Abbreviation: NA = not applicable.

A separate analysis was undertaken for those patients admitted in calendar year 2006 and newly started on ziprasidone. Of 3381 new admissions receiving antipsychotics, 249 (6.4%) were prescribed ziprasidone on the day of admission and, presumably, were receiving this agent at their prior hospital. One hundred twelve patients (3.3%) were newly started on treatment with ziprasidone after the day of admission (see Table 2 for the comparable rates observed in 2004 and 2005). The antecedent antipsychotic among new starts on treatment with ziprasidone did not show a specific pattern, with the 6 most frequent antipsychotics being quetiapine, risperidone, clozapine, olanzapine, haloperidol, and aripiprazole. The initial ziprasidone mean (SD) dose on the first day for new starts was 91 (48) mg/day, a value that represents a much higher starting dose than the 40 mg/day suggested in the product label.[5]

Interfacility variation regarding the utilization and dosing of ziprasidone was also explored for calendar day June 15, 2006. The utilization of ziprasidone among all the patients receiving antipsychotics that day was 5.8% at a mean dose of 186 mg/day, with 42.4% receiving a daily dose in excess of 160 mg (Table 4). Among the 16 inpatient psychiatric centers, the number of patients receiving antipsychotics ranged from 58 at the smallest facility to 494 at the largest. The percentage of patients receiving ziprasidone ranged from a low of 0.9% at one facility (1 of 114 patients) to 23.1% (18 of 78 patients) at another. The mean (SD) daily dose ranged from a low of 123 (57) mg among 6 patients at one facility to 311 (136) mg among 18 at another. It appears that the facilities that have higher rates of utilization of ziprasidone in general have higher rates of patients receiving ziprasidone in excess of 160 mg/day, which we determined by comparing the 8 highest-using facilities (1720 patients, 151 receiving ziprasidone) with the 8 lowest-using facilities (2027 patients, 66 receiving ziprasidone). The percentage of patients receiving ziprasidone in excess of 160 mg/day was 50.3% for patients in the high-use facilities versus 24.2% for those in the low-use facilities (relative risk = 2.08, 95% CI = 1.32 to 3.27).

DISCUSSION

Within the inpatient population served by the New York State Office of Mental Health, mean ziprasidone dosage has significantly increased over the span of time between 2001 and 2006, and the mean dose during the 2005 and 2006

Table 4. Characteristics of the Adult Inpatient Population Receiving Ziprasidone ≤160 mg/Day Versus >160 mg/Day on June 15, 2006[a,b]

Characteristic	Value		
Prescribed antipsychotic, N	3747		
Prescribed ziprasidone[c]	217 (5.8)		
Daily ziprasidone dose, mean (SD), mg/d	186 (83)		
	Patients Receiving Ziprasidone		
	All	≤160 mg/d	>160 mg/d
N	217	125	92
Male[d]	133 (61.3)	74 (59.2)	59 (64.1)
Nonwhite[d]	109 (50.2)	69 (55.2)	40 (43.5)
Age, mean (SD), y	44.2 (12.6)	44.4 (13.2)	43.8 (11.9)
Length of stay >360 days[d]	146 (67.3)	84 (67.2)	62 (67.4)
Schizophrenia or schizoaffective diagnosis[d]	170 (78.3)	94 (75.2)	76 (82.6)
Prior state admission[d]	149 (68.7)	85 (68.0)	64 (69.6)
Prescribed another antipsychotic[d]	125 (57.6)	71 (56.8)	54 (58.7)
Prescribed lithium or an anticonvulsant[d]	146 (67.3)	81 (64.8)	65 (70.7)
Ordered once daily[d]	19 (8.8)	13 (10.4)	4 (4.3)

[a]Results similar for March 15, 2006, September 15, 2006, and December 15, 2006 (not displayed).
[b]Values expressed as N (%) unless otherwise noted.
[c]Among all patients receiving antipsychotics on the specified calendar day.
[d]Among all patients receiving ziprasidone at the specified dose category on the specified day.

reporting period is higher than the dose recommended by the manufacturer. The dosing pattern for ziprasidone mirrors what was observed for quetiapine in the same population[3] in that, for both ziprasidone and quetiapine, the mean dose used is higher than the target dose range recommended in product labeling and substantial proportions of patients receive doses in excess of the highest recommended dose. Moreover, patients receiving ziprasidone or quetiapine as antipsychotic monotherapy or in combination with other antipsychotics were at least equally likely to receive doses in excess of the highest recommended amount.

It is possible that when ziprasidone first became available, it was used at lower doses because clinicians were influenced by marketing materials in 2001 that emphasized that the initial dose be 40 mg/day in divided doses "to initiate control" and that, after a period of evaluation, the clinician can "optimize response" by dosing within the range of 40 to 160 mg/day.[16] Moreover, perhaps clinicians were concerned about the bolded warning in the product label regarding QT prolongation and risk of sudden death.[5] However, it appears that, with more experience and the absence of high rates of adverse events, clinicians became more at ease with higher dosages. Supporting this is the observation of greater use of ziprasidone doses in excess of 160 mg/day among higher-use facilities in the New York hospital system. The continued use of high dosing over time may relate to the severity of illness commonly found among patients hospitalized in state institutions. This observation raises the possibility that, in subgroups of patients with prior partial response, ziprasidone may need to be dosed at higher than the product-label maximum of 160 mg/day. This is an important departure from the product label notation that 40 mg/day may be adequate for the maintenance treatment for schizophrenia.[5]

The finding that higher doses of ziprasidone were more frequently administered to patients with a prior history of state hospital admission was also found in our population for quetiapine dosing[3] and is consistent with the idea that these patients may be more chronically ill and perhaps require higher doses to achieve acceptable symptom control.

Patients receiving ziprasidone as antipsychotic monotherapy or in combination with other antipsychotics were essentially equally likely to receive doses in excess of 160 mg/day. These results are counterintuitive if one assumes that combination treatment is used in order to decrease the individual doses of each of the administered medications. However, it is also possible that patients who have inadequate symptom control would receive multiple medications at the highest tolerated dose in an effort to manage their illness.

Although positron emission tomography studies of D_2 receptor occupancy predict that ziprasidone doses of approximately 120 mg/day appear necessary to achieve sufficient dopamine blockade to reduce psychotic symptoms,[17,18] whether or not higher doses of ziprasidone are more efficacious than lower doses requires information from fixed-dose, randomized clinical trials.[19] There are 5 published double-blind clinical trials on schizophrenia that have used fixed-doses of ziprasidone up to 160 mg/day[20–24] and an unpublished study that included a ziprasidone 200 mg/day arm, which was described in a medical letter from the manufacturer (Pfizer, Inc., March 14, 2008) and in the product label.[5] These studies, taken individually, have not provided consistent evidence of a dose-response relationship, with 3 short-term (4 or 6 weeks) studies[20–22] suggesting a dose-response and 2 longer-term (12 or 24 weeks) studies (Kinon et al.[23] and Pfizer, Inc., medical letter, March 14, 2008) and one 1-year relapse study[24] suggesting otherwise. However, by pooling all available data in a meta-analysis, Davis and Chen[25] determined that the threshold dose range necessary to produce all or almost all the clinical responses for ziprasidone is approximately 120 to 160 mg/day for treating acute schizophrenia and 80 to 120 mg/day for maintenance treatment.

Although not controlled or fixed-dose, observational studies that provide additional information are available. Providing a low initial prescribed dose may result in a higher rate of discontinuation, as evidenced among adult Medicaid recipients diagnosed with schizophrenia or schizoaffective disorder and prescribed ziprasidone, in which case a start with a high dose (120–160 mg/day) was associated with a 20% lower risk of discontinuation than with a low dose (20–60 mg/day).[26] This finding was essentially replicated by a study of similar design among individuals diagnosed with

schizophrenia or schizoaffective disorder who were insured principally by commercial health insurance plans.[27]

Complicating the interpretability of observational studies is that ziprasidone should be administered with a meal because bioavailability is reduced by as much as 50%[5] when ziprasidone is not taken with food.[28] In essence, under fasting conditions, increases in area under the serum concentration-time curve and maximum drug concentration are less than dose proportional; however, under fed conditions, they are dose proportional with less pharmacokinetic variability.[29] The difference in serum concentrations between fasting and fed states becomes more marked at higher oral doses. In randomized clinical trials with sufficient patient supervision, such as in a hospital setting, ziprasidone administration occurs with food, but there is no assurance that taking ziprasidone with a meal occurs routinely in clinical practice. This may also be a concern in controlled studies conducted with outpatients responsible for their own medication administration.

There are no published randomized controlled studies of ziprasidone at doses that exceed 160 mg/day. However, several case reports and series are available that describe the potential benefits and drawbacks of higher dosing in schizophrenia and in other disorders. In general, it appears that there is a therapeutic benefit from using a high dose, with little downside in terms of tolerability. In a retrospective electronic record review of 106 inpatients and outpatients with schizophrenia or affective spectrum disorders receiving ziprasidone in doses greater than 160 mg/day up to a maximum of 640 mg/day, the most common dosages were 240 mg/day (N = 45) and 320 mg/day (N = 41), and almost all patients had a trial at a dose of 160 mg/day before being increased to dosages higher than 160 mg/day.[30] A higher dose of ziprasidone was associated with improvement in psychopathology and was generally well tolerated. There was no significant relationship between dose and adverse events. Similar outcomes were reported in a report of 4 cases of high-dose ziprasidone monotherapy in patients with bipolar I disorder with depressed or mixed episodes, in which cases doses of 480 mg/day, 200 mg/day, 240 mg/day, and 320 mg/day were utilized.[31] However, there is a case report of a patient with schizophrenia who developed acute dystonic reactions when taking ziprasidone 240 mg/day, even though she did not display any extrapyramidal symptoms with ziprasidone 160 mg/day taken for several months.[32]

Despite initial concerns regarding QT prolongation when ziprasidone was initially introduced, this has not materialized into a significant clinical problem.[33] This seems to be the case even when doses above 160 mg/day have been used. The effect of high-dose ziprasidone on electrocardiograms was specifically assessed in a retrospective study of 15 inpatients who had received ziprasidone 240 to 320 mg/day for intractable psychotic symptoms, with no significant increase in risk of QTc prolongation observed.[34]

Complicating the marketing of ziprasidone are the different recommended dosing schedules for the treatment of bipolar mania as compared to schizophrenia. Advertisements for ziprasidone's use in bipolar disorder in 2005 mirrors the product labeling, which recommends an initial dose of 80 mg/day, with titration to 120 to 160 mg/day on day 2 of treatment.[5,35] It is possible that clinicians may have generalized this guidance to patients with schizophrenia, even though this dose-titration schedule would technically be "off-label" for the treatment of schizophrenia. In 2008, information on dosing for schizophrenia in advertisements gives a dosing target of "120–160 mg/day with meals" but includes the caveats "initiate at 40 mg/day" and the "lowest effective dose should be used."[36]

Limitations

Whether or not ziprasidone was ordered to be administered with meals could not be ascertained in the IRDB. Mention of meals could not be found in either the dose or frequency data fields of the IRDB. It is possible that medication administration with meals was explicit in the original handwritten doctors' orders but that these were not entered into the pharmacy database.

Data regarding co-prescribing of ziprasidone with other medications is limited in that only 1-day "snap-shots" were used to assess this. The length of time the co-prescription occurred was not determined. The rates of co-prescription we report here are likely to be higher than rates calculated using other definitions of co-prescribing that specify a minimum period of overlap for the medication orders of interest.[11]

Our population consists of the chronically mentally ill, with 66% having had a prior psychiatric hospitalization in the same system of care and over 40% having a length of stay greater than 360 days. The results presented here may not be generalizable to first-episode patients, to those who are less severely ill, or to patients not requiring inpatient hospitalization. We were unable to find published reports of ziprasidone dosing over time among outpatients, although there have been non–peer-reviewed poster presentations of dosing data from outpatients enrolled in commercial, Medicare, and Medicaid health plans describing increases in mean daily dose from 2001 to 2006, such as from 100 mg/day to 130 mg/day among commercial enrollees,[37] and an increase in initial use of doses that exceed 160 mg/day,[38] but no trend in overall proportion of treatment episodes over time above 160 mg/day was noted.[38]

Future Directions

Whether higher doses are helpful or not cannot be answered by the "practice-based evidence" that higher doses of certain agents are routinely used. Although outpatients responsive to treatment may benefit from a dose range of ziprasidone with an upper limit of 160 mg/day as recommended in the product label,[5] there remains an urgent

need to conduct well-designed clinical trials that would address the question of whether or not there is an efficacy advantage when exceeding this recommended maximum and address the safety of ziprasidone when dosing at these higher levels.

One such study, among outpatients and inpatients with schizophrenia who have not adequately responded to ziprasidone 160 mg/day, is currently under way.[39] In this protocol, patients are randomly assigned to receive double-blind ziprasidone at either 160 mg/day or 320 mg/day for 8 weeks. This design mirrors clinical practice in which the dose of ziprasidone is increased beyond 160 mg/day in patients not responding to lower doses.

At the present time, the prescription of ziprasidone in excess of 160 mg/day in a patient with schizophrenia can be considered as a mini clinical trial with that patient. Specific target symptoms need to be identified and measured before starting the high-dose treatment and then periodically reassessed. If both the clinician and the patient cannot conclude that a substantial benefit is accruing, then this dosing strategy needs to be expeditiously discontinued.

CONCLUSIONS

Registration studies of ziprasidone have led to dosage recommendations that differ from clinical practice in a state hospital population. Initial recommendations for a target range of 40 to 160 mg/day for patients with schizophrenia have been overtaken by clinical practice in which doses in excess of 160 mg/day are routinely used among hospitalized patients with serious and persistent mental illness, either alone or, at times, in combination with other antipsychotics. Anecdotal reports have provided preliminary indications that doses in excess of 160 mg/day and up to 640 mg/day may be safe and efficacious. Because schizophrenia is often complex to treat, there remains a need for the clinician to be nimble enough to consider high-dose strategies, should doses of ziprasidone of 160 mg/day, administered with food, fail to be therapeutic. "Absence of evidence of efficacy" is not the same as "evidence of absence of efficacy," and, as a consequence, there remains the possibility that an individual patient may benefit from doses of ziprasidone that exceed 160 mg/day. However, this means the clinician must make an attempt to quantify improvement, help the patient assess the value of the treatment while balancing benefits and adverse effects, and be prepared to abandon the strategy if substantial advantages for the use of high-dose ziprasidone are not forthcoming. We look forward to the availability of results from controlled clinical trials that will clarify this use of ziprasidone.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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