Pancreatitis Associated with Atypical Antipsychotics: From the Food and Drug Administration's MedWatch Surveillance System and Published Reports

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Study Objective. To investigate the relative numbers and clinical characteristics of pancreatitis in patients treated with the atypical antipsychotic agents, clozapine, olanzapine, and risperidone, versus the conventional neuroleptic, haloperidol.

Design. Pharmacovigilance study of pooled, spontaneously reported adverse events.

Setting. Government-affiliated drug evaluation center.

Patients. One hundred ninety-two patients who developed pancreatitis during treatment with one or more antipsychotic agents.

Intervention. Patients were identified with the Food and Drug Administration's MedWatch surveillance program and a MEDLINE search.

Measurements and Main Results. Most cases of pancreatitis occurred within 6 months after the start of therapy with one or more antipsychotic agents. Of the reports of pancreatitis occurring in conjunction with these drugs, 40%, 33%, 16%, and 12% were in patients receiving treatment with clozapine, olanzapine, risperidone, and haloperidol, respectively. In 50% of the patients receiving haloperidol, an atypical antipsychotic was listed as a concomitant drug. Valproate was administered concomitantly in 23% of patients. Hyperglycemia and acidosis, although uncommon, developed with all the drugs except haloperidol. Twenty-two patients died. In contrast to patients who developed pancreatitis while receiving an atypical antipsychotic, those who developed the disease while receiving haloperidol were women and tended to be older.

Conclusion. The number of reports involving the three atypical antipsychotic agents and the relative paucity of reports involving haloperidol, despite its more extensive patient exposure, suggest that atypical antipsychotics may precipitate pancreatitis. However, the risk may not be the same with all agents; pancreatitis was reported most frequently with clozapine, followed by olanzapine, and then risperidone. The temporal relationship of the onset of pancreatitis with the start of drug therapy further supports a cause-and-effect relationship.

(Pharmacotherapy 2003;23(9):1123–1130)

OUTLINE

Pancreatitis is an inflammatory condition in which intrapancreatic activation of proteases results in autodigestion of the pancreas. Approximately 200,000 persons experience acute pancreatitis in the United States on an annual basis, and up to 30% of patients experience significant morbidity and/or mortality.[1] The associated pain can be debilitating, and hypotension and death can occur. Chronic pancreatitis may predispose patients to pancreatic malignancy.[2] Older patients and those who are obese appear to experience complications at a higher rate.[2, 3]

The process of autodigestion can be initiated by the obstruction of pancreatic ducts, increased pancreatic enzyme outflow, increased permeability of the ducts, impaired arterial flow, and direct cellular toxicity.[4] There are probably several mechanisms for cytotoxicity; for example, dideoxyinosine is thought to cause damage to mitochondrial DNA.[5] Other drugs that have been associated with pancreatitis are azathioprine, estrogen, thiazides, furosemide, sulfonamides, and pentamidine.[6–10]

Reports of pancreatitis occurring in association with the atypical antipsychotic clozapine were published in 1992[11, 12] and were followed by reports of pancreatitis associated with olanzapine.[13] Some of these cases were accompanied by varying degrees of new-onset hyperglycemia, another adverse event associated with the atypical antipsychotic agents.[14, 15] Before the introduction of the atypical agents, antipsychotics seldom were associated with pancreatitis. However, valproate, which may be administered concomitantly to stabilize mood or reduce risk of seizure in some neuroleptic patients, has been implicated.[7, 8, 16, 17]

To gain further insight into the clinical characteristics and the relative risk of pancreatitis associated with atypical antipsychotic agents, we queried the Food and Drug Administration (FDA) MedWatch database to identify reports of pancreatitis occurring in patients receiving therapy with clozapine, olanzapine, and risperidone and to compare them with reports of patients receiving the conventional neuroleptic agent, haloperidol.

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Methods

Clozapine and olanzapine were selected for assessment because of sporadically published case reports; we also assessed risperidone because it is widely prescribed. We did not study the relatively newer drugs, such as quetiapine and ziprasidone. Haloperidol was used as the control drug because it is not generally associated with pancreatitis despite its long prescription history and because it continues to be prescribed for many of the same patient populations. We identified cases of pancreatitis for all four drugs (regardless of administrative route, which was primarily oral) by querying the FDA's MedWatch Drug Surveillance System (January 1981–February 2002). Published reports were identified by searching MEDLINE (through February 2002).[18–31] We combined reports common to both systems. Drug use data were obtained through the National Prescription Audit *Plus*™ (IMS Health, Inc., Plymouth Meeting, PA) and the National Disease and Therapeutic Index Audit™ (IMS Health, Inc.).

We evaluated reports for documentation of pancreatitis, time to onset, patient demographics, concomitant hyperglycemia and/or acidosis, concomitant use of other antipsychotic drugs, and concomitant use of any other drugs. Cases were considered documented if supportive diagnostic data were present. Such data consisted of amylase and lipase levels, radiographic findings (ultrasound, magnetic resonance imaging, and computed tomography), surgical inspection with or without intervention, and therapy with pancreatic digestive enzymes.

Cases in which pancreatitis was reported, but the diagnostic rationale was not provided, were included but not classified as documented.

Patients whose reports suggested that they were receiving treatment with only one of the four antipsychotic agents were considered to be receiving monotherapy. Those who were treated with two or more of the four antipsychotic agents were considered to be receiving combination therapy, and their data were included in the calculations for each component of antipsychotic

Table 1. Demographic Patient Data from Case Reports of Antipsychotic-Associated Pancreatitis

Antipsychotic Agent	No. of Cases of Pancreatitis			Documentation[a] (no. of patients)	Age (yrs), Mean ± SD (no. of patients)[b]	Male:Female Ratio (no. of patients)[b]
	Total	U.S.	Foreign			
Monotherapy						
Clozapine	72	47	25	53	39.3 ± 13.0 (68)	1.3:1 (69)
Olanzapine	62	41	21	40	40.0 ± 14.2 (55)	1.4:1 (61)
Risperidone	31	26	5	17	42.8 ± 18.7 (30)	1:1 (30)
Haloperidol	12	4	8	6	48.8 ± 27.4 (10)	1:9 (10)
Combination therapy[c]						
Clozapine	10	9	1	6	36.2 ± 16.7 (9)	4:1 (10)
Olanzapine	7	5	2	6	38.0 ± 12.5 (7)	6:1 (7)
Risperidone	2	1	1	1	46.0 ± 35.4 (2)	0:2 (2)
Haloperidol	12	10	2	8	39.3 ± 19.2 (11)	1.4:1 (12)

[a]Documentation was present for the diagnosis of pancreatitis.
[b]Number of patients for whom data were available.
[c]Combination therapy is defined as the drug listed plus one of the other two atypical antipsychotic agents or haloperidol. The most frequently prescribed concomitant drug was haloperidol.

therapy. Other psychiatric drugs could be administered in either treatment classification. For patients whose dosage was changed, the maximum daily dose was used in our assessment. Concomitant drugs were grouped into one of the following four categories: included valproate, included drugs other than valproate, none, or unknown. Because valproate has been associated with pancreatitis, its administration was evaluated separately.

The nature of spontaneously reported adverse events limited the uniformity and completeness of the information, and we have specified where data were missing. Of note, haloperidol was approved and marketed before the current MedWatch surveillance system was implemented. Demographics and sales data were obtained from IMS Health, a commercial entity that provides market research data on drug utilization. Drug exposure was estimated from cumulative numbers of prescriptions (National Prescription Audit *Plus*™) and the mean duration of a prescription for the antipsychotic (National Disease and Therapeutic Index Audit™). Drug appearance data are the source of demographics for a pharmaceutical compound and those who receive the compound. These data are based on sampling information for prescriptions, refills, and drug samples dispensed during medical office visits or hospital stays. They reflect treatment intent of the physician and not actual patient behavior or compliance. In addition, the estimates for the haloperidol drug administration data are further limited by changes in the collection methodology over time, and the absence of complete numeric prescription data from the 1970s.

As such, this is a descriptive report based primarily on summary statistics. We used correlation coefficients and unpaired *t* tests (all two-tailed) to assess the relationship between certain variables or groups; p values less than or equal to 0.05 were deemed significant. Estimates of patient exposure were based on the number of prescriptions and average duration of a prescription. Reporting rates were determined from the number of U.S. reports divided by the estimated patient exposure for that drug. (Reporting rates differ from incidence rates but can provide information on the relative frequency of an event.) Conservative reporting rates for each antipsychotic agent were determined from all patients receiving that particular drug, whether as monotherapy or combination therapy. More selective reporting rates were determined for patients receiving monotherapy alone. To estimate relative risk, ratios of reporting rates for the various atypical antipsychotic agents and haloperidol were determined. The reporting rate ratios derived from all-use data were compared with reporting rates from the more selective monotherapy data to assess consistency between the two data sets.

Results

We identified 192 cases of pancreatitis; 18 of these were reported in 17 publications. Of these reports, 131 originated in the United States and 61 were from foreign sources (Table 1).

Nature of Pancreatitis Reports

Seventy-two cases of pancreatitis occurred in patients receiving clozapine monotherapy (Table 1).

An additional 10 cases occurred in patients receiving clozapine plus olanzapine, risperidone, and/or haloperidol. Sixty-two cases occurred in patients receiving only olanzapine, with an additional seven cases in patients receiving olanzapine plus clozapine, risperidone, and/or haloperidol. Thirty-one cases occurred in patients receiving only risperidone, with an additional two cases in patients receiving risperidone plus haloperidol. Twelve cases occurred in patients receiving haloperidol monotherapy. Another 12 occurred in patients receiving haloperidol plus one or more of the three atypical antipsychotics. Only two of the reported haloperidol cases (one U.S., one foreign) occurred before 1991. An additional three monotherapy cases (all foreign) and three combination therapy cases (all U.S.) occurred before 1996.

Documentation for the diagnosis of pancreatitis was provided in most cases: clozapine 72% (59 of 82 cases), olanzapine 67% (46 of 69), risperidone 54% (18 of 33), and haloperidol 58% (14 of 24). Only three cases were documented in which concomitant acidosis or ketosis could confound diagnoses based on hyperamylasemia alone. The antipsychotic drug (one or more with combination therapy) was discontinued in 60% of patients (clozapine 67% [55 of 82 patients], olanzapine 64% [44 of 69], risperidone 56% [19 of 33], and haloperidol 21% [5 of 24]), although the period of discontinuation was often brief.

Patient Demographics

Mean ± SD ages of patients with pancreatitis who were receiving clozapine, olanzapine, risperidone, and haloperidol, alone or in combination, were 38.9 ± 13.4, 39.7 ± 14.0, 43.0 ± 19.2, and 43.8 ± 23.4 years, respectively (Table 1). Although the patients treated with haloperidol alone were older than those treated with haloperidol in conjunction with an atypical antipsychotic agent, the differences did not reach statistical significance (p=0.37). Similarly, the mean age differences between patients receiving haloperidol versus an atypical antipsychotic did not reach statistical significance. Ten pediatric patients were affected: four (aged 15, 16, and 18 yrs, and an unspecified adolescent) were treated with olanzapine, three (aged 10, 13, and 16 yrs) with risperidone, one (aged 15 yrs) with clozapine, one (aged 17 yrs) with haloperidol, and one (aged 17 yrs) with a combination of clozapine and haloperidol.

A slight male predominance was noted in those treated with clozapine, olanzapine, and haloperidol in combination with an atypical antipsychotic agent (Table 1). These sex differences were absent with risperidone. These findings contrast with the female predominance observed with haloperidol monotherapy.

Time to Diagnosis of Pancreatitis and Antipsychotic Daily Dose

Time-to-diagnosis information was available for 82% of patients; sometimes, however, information was available for only one of the antipsychotic agents (10 patients). The time to diagnosis of pancreatitis in patients for whom such data were available was 6 months or less for most patients in all treatment groups: clozapine 63% (46 of 73 patients), olanzapine 63% (32 of 51), risperidone 79% (22 of 28), and haloperidol 90% (9 of 10).

Some dosing information was available for 81% of patients. For six patients, information was available on only one of the antipsychotic agents. The mean ± SD daily doses were clozapine 306.7 ± 202.9 mg (range 12.5–1000 mg, 73 patients), olanzapine 15.0 ± 6.3 mg (range 2.5–30 mg, 53 patients), risperidone 4.0 ± 3.7 mg (range 0.5–20.0 mg, 27 patients), and haloperidol 8.2 ± 7.7 mg, (range 0.5–20 mg, nine patients). There was no significant correlation between daily dose and the time to diagnosis. Drug levels, which may be more predictive of clinical effects, were not available.

Concomitant Drugs

Although completeness of the information is uncertain, concomitant drug information was provided for 82% (157 of 192) of patients. Reporting rates were similar for all drugs administered: clozapine 78% (64 of 82 patients), olanzapine 90% (62 of 69), risperidone 76% (25 of 33), and haloperidol 92% (22 of 24). The most commonly administered concomitant drugs were clonazepam, lorazepam, lithium, paroxetine, sertraline, thyroid hormone, and valproate, as well as various agents given to treat hypertension, diabetes, constipation, and peptic disease. Valproate was administered as a concomitant drug in a minority of patients: clozapine 34% (22 of 64), olanzapine 34% (21 of 62), risperidone 16% (4 of 25), and haloperidol 14% (3 of 22). Valproate reportedly also had been administered for extended periods in some patients whose pancreatitis did not develop until

after the start of antipsychotic therapy. Pancreatitis also occurred in the documented absence of concomitant drugs for eight patients receiving clozapine; seven, olanzapine; two, risperidone; and one, haloperidol.

Alcohol Consumption

Reporting of alcohol abuse was incomplete, but 11 patients were reported as current abusers. Perhaps more significant are the 39 reports in which patients had no recent history or any history of alcohol abuse: those receiving clozapine (6 patients), olanzapine (25), risperidone (6), haloperidol (1), and combined clozapine-olanzapine-haloperidol (1).

Comorbid Outcomes

Hyperglycemia

Pancreatitis sometimes occurred in patients with hyperglycemia. For clozapine, there were 16 reports of newly diagnosed hyperglycemia, such as one that occurred with a second episode of pancreatitis. There were two reports of an exacerbation of preexisting diabetes. For one patient, we could not determine whether the onset of hyperglycemia was new or an exacerbation of preexisting disease. For another patient, data were conflicting regarding potential new-onset diabetes. Follow-up with the psychiatric institution did not resolve the discrepancy in serial reports. Eight patients had preexisting diabetes that did not worsen with the pancreatitis; in two of these patients, hyperglycemia occurred after the start of clozapine therapy but before the onset of pancreatitis.

For olanzapine, there were 21 reports of newly diagnosed hyperglycemia. For another two patients, we could not determine whether the onset of hyperglycemia was new or an exacerbation of preexisting disease. An additional patient experienced diabetic ketoacidosis and unconfirmed pancreatitis with her first exposure to olanzapine followed by hyperamylasemia (amylase level 933 IU/L) and recurrence of ketoacidosis with reexposure. Five patients had preexisting diabetes that did not worsen with the pancreatitis; in one of these patients, hyperglycemia occurred subsequent to the start of olanzapine therapy but before the onset of pancreatitis.

For risperidone, four patients were reported with newly diagnosed hyperglycemia and one with an exacerbation of preexisting disease. Three patients had preexisting diabetes that did not worsen.

For haloperidol, no patients were reported with newly diagnosed hyperglycemia or an exacerbation of preexisting diabetes. Two had preexisting diabetes that did not worsen.

Acidosis

Sometimes pancreatitis occurred with acidosis that generally was associated with glucose abnormalities. Metabolic abnormalities ranged from mild ketosis to frank diabetic ketoacidosis. For clozapine, there were 11 reports of ketosis. For olanzapine, there were 13 reports of ketosis and one report of an unspecified type of metabolic acidosis. There was one report of ketosis in a patient receiving combined olanzapine-clozapine therapy. For risperidone, there were three reports of ketosis. For haloperidol monotherapy, there were no reports of acidosis. There was a single report of an unspecified type of metabolic acidosis in a patient receiving both haloperidol and clozapine.

Fatalities

Twenty-two patients died; one was a 15-year-old boy. In some patients, such as the 15-year-old boy, death was directly related to the pancreatitis. In other patients, the pancreatitis was a comorbidity. Frequently, the reported data were insufficient or the clinical picture was unclear, so that comorbidity and direct cause of death could not be distinguished. Of the 22 patients who died, seven received clozapine, nine olanzapine, two risperidone, and three haloperidol; one patient received both clozapine and haloperidol.

The demographics and clinical presentation of the patients who died did not differ substantially from those who survived. Of the patients with fatal outcomes who received atypical antipsychotics, mean ± SD age was 45.8 ± 17.0 years (range 15–74 yrs, 16 patients with data). Mean ± SD age of those with fatal outcomes who received haloperidol was 55.0 ± 46.7 years (range 22–88 yrs, two patients, both monotherapy cases, with data). Of the patients with fatal outcomes who received atypical antipsychotics, nine were women and nine were men. Of the remaining three with fatal outcomes who received haloperidol (monotherapy), two were women, and the sex of the third patient was unknown. A man who was receiving both clozapine and haloperidol also died. Eight patients who

Table 2. Reporting Rate Ratios for Patients with Pancreatitis Associated with Antipsychotic Drugs

Variable	Clozapine	Olanzapine	Risperidone	Haloperidol
Initiation of U.S. marketing (data through February 2002)	1991	1996	1994	1969
No. of prescriptions (in thousands)	15,082	22,154	31,748	67,681[a] 31,126[b] 22,159[c] 15,356[d]
Mean duration of therapy (days)[e]	16.4	34.8	35.7	35.1
No. of estimated patient-years of exposure (in thousands)	678.7	2104.6	3111.3	6497.4[a], 2988.1[b] 2127.3[c] 1474.2[d]
U.S. reporting rate ratios[f]; antipsychotics compared with haloperidol				
Monotherapy cases[g]				
Using haloperidol cases and exposure from 1981–February 2002[a]	112.5	31.6	13.6	1
Haloperidol cases and exposure limited to 1991–February 2002[b]	69.0	19.4	8.3	1
Haloperidol cases and exposure from calendar year the comparator drug was initially marketed through February 2002	69.0[b]	9.6[d]	5.9[c]	1[a]
All-use cases[h]				
Using haloperidol cases and exposure from 1981–February 2002[a]	38.3	10.1	4.0	1
Haloperidol cases and exposure limited to 1991–February 2002[b]	19.0	5.0	2.0	1
Haloperidol cases and exposure from calendar year the comparator drug was initially marketed through February 2002	19.0[b]	3.2[d]	1.5[c]	1[a]

[a]National Prescription Audit *Plus*™ data from 1981, time of first U.S. haloperidol case, through February 2002 were used. 1981–1992 data were derived from book sources and did not include mail order and long-term care data. Later data were derived from online sources.
[b]Numeric prescription data from 1991–February 2002 used to provide data for the same time frame as clozapine exposure.
[c]Numeric prescription data from 1994–February 2002 used to provide data for the same time frame as risperidone.
[d]Numeric prescription data from 1996–February 2002 used to provide data for the same time frame as olanzapine.
[e]National Disease and Therapeutic Index Audit™ data are from 1996–February 2002.
[f]Reporting rate = number of cases of pancreatitis reported/drug exposure.
[g]Monotherapy describes reports involving only one of the antipsychotic drugs being studied.
[h]All-use refers to all reports in which the drug was administered either as monotherapy or in combination with one or more of the antipsychotic drugs studied.

received atypical antipsychotics and died were reported to have received valproate concomitantly. None of the deceased patients who received haloperidol, including the patient who received both clozapine and haloperidol, received valproate concomitantly. One of patients who received haloperidol reportedly received no other drug.

For the deceased patients who received atypical antipsychotics, including the patient who received both clozapine and haloperidol, time to onset of pancreatitis was 6 months or less for 72% (13 of 18 patients for whom time-to-onset data were available). Four cases occurred within 8 days of the start of drug therapy. For two patients who received haloperidol, time to onset was less than 11 days. Information regarding time to onset was not provided for two patients receiving haloperidol; one was the patient who received combination therapy. Seven of the deceased patients who received atypical antipsychotics had experienced new-onset diabetes or an exacerbation of preexisting diabetes. No deceased patients who received haloperidol had such deterioration in glycemic control. Five patients who received atypical antipsychotics had ketosis or frank ketoacidosis. In addition, one patient who received the combination clozapine-haloperidol therapy had an unspecified type of metabolic acidosis. None of the patients who received haloperidol monotherapy was reported to be acidotic.

Reporting Rates

Estimates of exposure to antipsychotic agents were lowest for patients receiving clozapine and highest for those receiving haloperidol (Table 2). Moreover, the calculated exposure to haloperidol is an underestimate because it does not incorporate data from the first decade of marketing the drug. The reporting rates for pancreatitis were comparatively higher for the atypical antipsychotic agents than for the conventional neuroleptic agent, haloperidol. The reporting rate ratios for clozapine were the highest. This was evident whether the calculations were based on all-use or mono-therapy

data. The reporting rate ratios increased approximately 3-fold when only those patients treated with a single antipsychotic were included in the analyses. The same interdrug differences in reporting rate ratios were observed whether the haloperidol-exposure data were limited to 1991 and beyond or were more inclusive, with data from 1981–2002.

Discussion

An association between atypical antipsychotic agents and the occurrence of pancreatitis was suggested by isolated case reports. Our systematic review of the FDA's MedWatch database and of the literature further solidifies this hypothesis. The number of cases of pancreatitis associated with each of the three atypical antipsychotics that we reviewed—clozapine, olanzapine, and risperidone—exceeded the number of cases associated with haloperidol. The disparity was even greater with patients receiving monotherapy; that is, when only one of the four antipsychotic agents studied was evaluated. This disparity was present despite the longer period of marketing for haloperidol.

Temporal changes in administration of a drug—versus the treated population or the extent of combination therapy with other agents, such as lithium—could alter the risk for a given adverse event. However, the disparity in reporting cases of pancreatitis in patients receiving the three atypical antipsychotic agents and haloperidol persisted even when the evaluation period was limited to 1991–2002. The data also suggest that the reporting rates for pancreatitis were not uniform for the various atypical antipsychotic agents. Finally, a temporal relationship existed between the start of drug therapy and onset of pancreatitis, which is a key element in establishing cause and effect.

Nonetheless, pancreatitis, a relatively uncommon disorder, has causes other than prescription drugs. Alcohol consumption is a known cause of the disease, and substance abuse occurs frequently in patients with schizophrenia, bipolar disease, and other psychiatric disorders. Although confounding substance abuse was present in some patients, it was not present in others. Rates of substance abuse may differ between users of various drugs. Indeed, IMS Health data suggest that proportionately more haloperidol and risperidone than olanzapine and clozapine are prescribed for geriatric patients, especially women. The IMS Health demographic data, however, do not explain the relative differences in risk for pancreatitis between olanzapine and clozapine.

In addition, if the rate of substance abuse in patients with psychotic disorders has remained stable, there is no explanation for the relative paucity of haloperidol-associated pancreatitis (two patients) reported in the 1980s before the introduction of the atypical antipsychotic drugs. Concomitant administration of valproate, which is thought to cause pancreatitis by an idiosyncratic reaction,[16] cannot explain most of the pancreatitis cases in our series, nor can the other reported concomitant drugs. Only 23% of our patients with pancreatitis had received valproate concurrently; of these, some had been treated with valproate for extended periods without experiencing pancreatitis. Adding an antipsychotic agent appeared to precipitate an attack of pancreatitis. Although addition of atypical antipsychotic drugs may enhance valproate's idiosyncratic toxicity to the pancreas, the nature of any such interaction remains to be defined.

Unfortunately, although studies have identified patients with recurrent pancreatitis on rechallenge,[22, 25] the standard dechallenge and rechallenge testing cannot be employed reliably in patients with pancreatitis because once significant activation of digestive enzyme has occurred, the process may not be reversible. Nonetheless, an observational study of a single patient may provide some insights.[20] The investigators followed serial amylase and lipase levels during titration of clozapine. Dosages were maintained when enzymes increased, and pancreatic enzyme levels subsequently returned to normal. The authors speculated that subclinical pancreatitis in patients receiving clozapine is more common than is clinically recognized, and that time can facilitate adaptation to the drug.

Other mechanistic data are lacking. Furthermore, although one group of investigators have shown that hemorrhagic pancreatitis induced by alcohol and pancreatic enzymes in cats is mediated by dopaminergic and β-adrenergic receptors in cats,[32] it is not known whether the effects of haloperidol and the atypical antipsychotic agents can be differentiated. This model does not appear to be predictive of nonalcoholic pancreatitis.

Conclusion

Although analysis of MedWatch reports cannot

provide definitive ascertainment of causality, the reporting rates for pancreatitis appear to be greater with the three atypical antipsychotics we reviewed—clozapine, olanzapine, and risperidone—than for the conventional antipsychotic, haloperidol. The reporting rates for pancreatitis, however, are not uniform for the three atypical antipsychotic agents. This complication was reported most frequently with clozapine, followed by olanzapine, and then risperidone.

Prospective studies with comparative frequency data will better define the absolute and relative risk associated with each of these agents and determine whether the relatively low reporting rates observed with haloperidol are found with other conventional neuroleptic agents. Prospective studies also may identify the clinical characteristics of patients who have the highest risk for developing pancreatitis. Because of the potential for death or chronic complications of pancreatitis, and because of the potential for reversibility, clinicians should be alert to this adverse event in patients who exhibit signs and symptoms of an acute abdominal disorder.

Acknowledgments

The authors are grateful to the health care professionals, patients, and family members of patients who submitted MedWatch forms and especially to those who provided follow-up information. The authors also express appreciation to Lanh Green, Carol Pamer, and Joslyn Swann for their help in procuring the adverse event reports and the IMS Health data.

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