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Original Article

Adverse Drug Reactions: A Retrospective Review of Hospitalized Patients at a State Psychiatric Hospital

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Abstract

Background: There is a paucity of information regarding adverse drug reactions (ADRs) in psychiatric patients. Information on common and preventable ADRs (pADRs) in psychiatric patients will allow for targeted improvement projects.

Objective: To characterize reported ADRs and pharmacist interventions to prevent ADRs in an extended-care state psychiatric hospital.

Methods: Four years of ADR reports were assessed for probability, reaction severity, pharmacological class of medication involved, preventability, change in therapy, and transfers to a medical facility. The pharmacist intervention database was queried for interventions classified as "prevention of ADR." The interventions were assessed for type of medication and recommendation acceptance.

Results: Medication classes responsible for ADRs included mood stabilizers (30%), typical antipsychotics (25%), atypical antipsychotics (25%), and antidepressants (8%). Nine percent resulted in transfer to a medical facility. Of all ADRs, 34.4% were pADRs; mood stabilizers (41%) and atypical antipsychotics (27%) were the most common pADRs. The most common causes of pADRs were supratherapeutic serum concentrations, drug-drug interactions, and history of reaction. There were 87 pharmacist interventions that were classified as "prevention of ADR," and the acceptance rate of pharmacists' recommendations was 96.5%. Mood stabilizers (20%), atypical antipsychotics (17%), and typical antipsychotics (11%) were commonly associated with prevented ADRs. Lithium accounted for 13.8% of prevented ADRs; these ADRs were most often due to a drug–drug interaction with a nonsteroidal anti-inflammatory drug.

Conclusions: ADRs were most commonly associated with mood stabilizers and antipsychotics, and pADRs were common. There is an opportunity to provide education to medical staff on therapeutic drug monitoring and drug–drug interactions for these classes, particularly lithium.

Key Words—adverse drug reactions, drug interactions, drug safety, preventable adverse drug reactions, psychiatry, psychotropic drugs

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Preventing and identifying adverse drug reactions (ADRs) in all patients is crucial to ensuring safe patient care. Although information regarding ADRs in medical hospital inpatients abounds, knowledge about the tolerability of psychotropic agents in psychiatric inpatients is sparse.[1-7] ADRs have not been studied as extensively in hospitalized psychiatric patients, as these patients may present challenges not seen in the nonpsychiatric patient population. For example, it may be difficult to distinguish antipsychotic-induced akathisia from underlying anxiety. Psychiatric patients also may have limited insight into their illness and

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limited knowledge about their treatment, which can lead to subjective complaints that may be difficult for a clinician to assess.[1]

ADRs in hospitalized psychiatric patients are not only common, but they also have a high rate of preventability.[2-3] Thomas et al[2] found that 20.4% of reported ADRs over a 3-year period in a state psychiatric hospital were preventable. Their study also found that psychiatric medications were responsible for 48.4% of ADRs. Rothschild et al[3] found that preventable ADRs (pADRs) accounted for 13% of all ADRs in a psychiatric hospital and that atypical antipsychotics accounted for 37% of all ADRs. Popli et al[4] studied the transfer of psychiatric patients to a medical hospital due to ADRs. They found that transfers were not frequent, but 76% of the transfers involved neurological reactions, including delirium, seizures, and syncope, and 32% of transfers involved the use of more than 1 psychotropic drug.[4]

A health care system can use data on frequency, severity, probability, and preventability to identify medications that should be targeted for quality improvement projects and patient education. Targeting high-risk medications that have been identified through analysis could have a significant impact on reducing preventable ADRs.

METHODS

A retrospective review was conducted of ADR reports from August 2007 to August 2011 at an academic state psychiatric hospital. Before 2009, the hospital included psychiatric emergency services, acute care, and extended care. From 2009 onward, the hospital has had only extended-care psychiatric services. The hospital currently uses a voluntary, spontaneous reporting system of ADRs; nurses, physicians, and pharmacists are all able to report ADRs. A standardized reporting form is used for these reports. Pharmacists also actively review all laboratory results and medication orders for indications that an ADR has occurred, such as an order for an anticholinergic medication to treat acute dystonia or a toxic serum level for lithium. When an ADR is suspected, the clinical pharmacist conducts a review using a standardized reporting form. Clinical pharmacists also enter all interventions, including ADR reports and interventions to prevent ADRs, into an internal online computer database.

The hospital uses the American Society of Health-System Pharmacists' definition of an ADR as any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuation of the suspected drug, changing the drug therapy (including dose modifications), or admission to a hospital.[8] Side effects are defined as known reactions to a drug requiring little or no change in therapy, and these are not categorized as ADRs.[8] Standardized reporting forms were used to analyze reported ADRs, and the online database was queried for interventions designated as "prevention of ADR." The Naranjo probability scale[9] was used to assess the probability that an ADR was due to a specific medication; probable and definite ADRs were included in this evaluation. Probable and definite ADRs were further classified according to medication class involved, severity, and preventability. Preventability was assessed using criteria proposed by Shumock et al[10] (**Table 1**). Severity was defined according to the following: mild ADRs did not require antidote, treatment, or increased length of stay; moderate ADRs required a specific antidote or treatment, a change in therapy, or increased length of stay; severe ADRs were life-threatening or required transfer to a medical facility for further medical care.

Statistical analysis was descriptive in nature. Total numbers of ADRs, pADRs, and severity ranks were summed and further classified according to medication class involved. pADRs were assessed for reason for preventability. Rate of preventability was determined by dividing the number of pADRs by the total number of ADRs and multiplying by 100. Pharmacist interventions were assessed for medication class involved, reason for

Table 1. Adverse drug reaction preventability criteria[a10]

1. Was the drug not considered appropriate for the patient's clinical condition?
2. Was the dose, route, and/or frequency of administration not appropriate for the patient's age, weight, and/or disease state?
3. Was required monitoring (therapeutic drug monitoring, laboratory tests) not performed?
4. Was there a history of previous reaction or allergy to the suspected medication?
5. Was a drug interaction involved?
6. Was a supratherapeutic serum concentration documented?
7. Was poor patient compliance involved?

[a]Answering yes to one or more of these questions classifies the adverse drug reaction as preventable.

preventability, and physician acceptance of recommendation.

The study was conducted in compliance with the Missouri Department of Mental Health Professional Review Committee, Center for Behavioral Medicine Hospital Review Committee, and the University of Missouri–Kansas City Adult Health Sciences Institutional Review Board.

RESULTS

Between August 2007 and August 2011, 115 ADRs were reported. Of these 115 ADRs, 64 were classified as probable or definite and were included in the analysis; 87.5% of ADRs were due to a psychiatric medication (antipsychotic, antidepressant, mood stabilizer, benzodiazepine, or stimulant). The medications most frequently associated with ADRs were divalproex sodium (15.6%) and haloperidol (12.5%). During this timeframe, divalproex sodium was the sixth most commonly used medication at this facility and haloperidol was the fifth most frequently used, based on number of doses dispensed. **Table 2** shows the complete breakdown of reported ADRs by medication class. The majority of all probable or definite ADRs were moderate (86%) or severe (12.5%); 96.9% resulted in a change in therapy and 9% resulted in transfer to a medical facility. Movement disorders were the most common ADR and accounted for 25% of all ADRs (acute dystonia, 12.5%; akathisia, 7.8%; pseudoparkinsonism, 4.7%). Other common ADRs were prolactin effects such as galactorrhea and gynecomastia (14.1%), neutropenia (7.8%), rash (6.2%), and hypersalivation (6.2%).

Eight ADRs were classified as severe; 3 were due to divalproex sodium (toxicity, hyperammonemia, transaminitis). Of additional severe ADRs, there were 2 cases of angioedema due to lisinopril, 1 case of neurotoxicity due to a drug–drug interaction with lithium, 1 case of a seizure related to a drug–drug interaction with fluoxetine, and 1 case of severe constipation and bowel obstruction requiring surgery due to clozapine. All severe ADRs resulted in change in therapy, and 75% resulted in transfer to a medical facility.

Preventable ADRs accounted for 29.7% (n = 19) of all ADRs. All pADRs resulted in change in therapy, and 21% resulted in transfer to a medical facility. **Table 2** provides a breakdown of preventable ADRs by medication class. The medication most often associated with a preventable ADR was divalproex sodium (n = 6) followed by lithium (n = 3). Drug–drug interactions (n = 8), supratherapeutic serum concentrations (n = 8), and history of previous reaction/

Table 2. Medications involved in adverse drug reactions and preventable adverse drug reactions in psychiatric inpatients

Total adverse drug reactions (n = 64)	
Psychiatric medications, n (%)	*56 (87.5%)*
Mood stabilizers (lithium, divalproex sodium, lamotrigine)	17 (26.6%)
Antipsychotics, second generation	17 (26.6%)
Antipsychotics, first generation	15 (23.4%)
Antidepressants	5 (7.8%)
Other (diazepam, mixed amphetamine salts)	2 (3.1%)
Nonpsychiatric medications, n (%)	*8 (12.5%)*
Antihypertensives (lisinopril)	2 (3.1%)
Antiepileptics (oxcarbazepine)	2 (3.1%)
Miscellaneous (benztropine, niacin, permetherin, simvastatin)	4 (6.2%)
Preventable adverse drug reactions (n = 19; 29.7% of all ADRs)	
Psychiatric medications, n (%)	*18 (94.7%)*
Mood stabilizers (lithium, divalproex sodium)	9 (47.4%)
Antipsychotics, first generation (chlorpromazine, haloperidol, loxapine)	4 (21.1%)
Antipsychotics, second generation (clozapine, risperidone, ziprasidone)	3 (15.8%)
Antidepressants (fluoxetine)	1 (5.3%)
Other (diazepam)	1 (5.3%)
Nonpsychiatric medications, n (%)	*1 (5.3%)*
Simvastatin	1 (5.3%)

allergy (n = 4) were responsible for the majority of pADRs. Fifty percent of severe ADRs were deemed preventable due to supratherapeutic serum concentrations and lack of required monitoring.

One hundred two pharmacist interventions were reported as "prevention of ADR" in the database. Of these, 87 had sufficient information to be analyzed. The rate of physician acceptance of the pharmacist's recommendation was 96.5%. Preventability criteria involved in recommendations were medication considered inappropriate for patient's age, weight, disease state, or clinical condition (n = 16); drug–drug interactions (n = 15); inappropriate dose (n = 15); recommendation for required monitoring (n = 8); and history of allergy or previous reaction (n = 7). **Table 3** provides a breakdown of prevented ADRs by medication class. Lithium accounted for 13.8% of all prevention of ADR recommendations. Seventy-five percent of recommendations regarding lithium involved a drug–drug interaction with a nonsteroidal anti-inflammatory drug.

DISCUSSION

This evaluation of ADRs in a state psychiatric hospital found that 87.5% of ADRs were caused by psychiatric medications. Thomas et al[2] also studied ADRs in a state psychiatric hospital and found that psychiatric medications were only responsible for 48.4% of ADRs, which is much lower than results from our study. The medication classes most frequently associated with ADRs in our study were mood stabilizers (including the antiepileptics used for mood stabilization), second-generation antipsychotics, and first-generation antipsychotics. Similarly, Thomas et al found antiepileptics and second-generation antipsychotics to be common causes of ADRs, although they also found cardiovascular agents to be a common cause.[2] Although other studies in psychiatric patients have not been conducted in state psychiatric hospitals, they also found psychiatric medications likely to be responsible for ADRs.[1,3] Of the 20 most frequently used medications at this facility based on number of doses dispensed, 10 are psychiatric medications. Thus, psychiatric medications appear to account for a larger percentage of ADRs than what would be expected based upon usage.

Table 3. Medications involved in prevented adverse drug reactions

Psychiatric medications, n (%)	*56 (64.4%)*
Mood stabilizers	16 (18.4%)
Antipsychotics, second generation	15 (17.2%)
Antipsychotics, first generation	10 (11.5%)
Benzodiazepines	7 (8.1%)
Antidepressants	6 (6.9%)
Stimulants	2 (2.3%)
Nonpsychiatric medications, n (%)	*31 (35.6%)*
Antihypertensives (amlodipine, lisinopril, propranolol)	6 (6.9%)
Anticholinergic agents (diphenhydramine, hydroxyzine)	5 (5.7%)
Nonsteroidal anti-inflammatory drugs (naproxen, ibuprofen)	4 (4.6%)
Cholesterol-lowering agents (gemfibrozil, niacin, simvastatin)	4 (4.6%)
Glycemic control agents (regular insulin, metformin)	2 (2.3%)
Antiepileptics (topiramate, gabapentin)	2 (2.3%)
Other (acetaminophen, acetazolamide, levothyroxine, naltrexone, omeprazole, prednisone, sumatriptan, thalidomide)	8 (9.2%)

The rate of pADRs was found to be 29.7%, which is higher than the rate currently reported in the literature. Thomas et al[2] found a preventability rate of 20.4% over a 3-year period, whereas Rothschild et al[3] found the rate to be 13% over a 6-month period. Preventability was defined by the same criteria in our study and the Thomas et al study[2]; however, in the Rothschild study, it was defined as any ADR associated with a medication error.[3] This difference in definitions could account for the difference in preventability rates between our study and the Rothschild et al study. Our study also found that severe ADRs had a higher rate of preventability (50%) compared to all ADRs. Severe ADRs were more likely to result in a change in therapy and transfer to a medical facility. Total ADRs in this study found a rate of transfer to a medical facility of 9%, whereas severe ADRs had a transfer rate of 75%.

Divalproex sodium was the medication most often associated with ADRs and pADRs in the current study. Haloperidol was also frequently associated with ADRs. It is interesting to note that lorazepam and clonazepam are the most commonly dispensed psychotropic medications; however, they did not have any ADRs reported during this 4-year timeframe.

A review of the literature did not show any published studies focusing on pharmacist interventions to prevent ADRs in psychiatric hospitals. Our data indicate that pharmacists frequently make interventions to prevent ADRs in this facility. Although there were 19 missed intervention opportunities in the form of pADRs, 102 pharmacist interventions to prevent ADRs were reported during a 4-year period. Pharmacist

recommendations were frequently accepted by physicians and involved medications that were clinically inappropriate, drug–drug interactions, and recommendations for monitoring. These data indicate that pharmacists play a valuable role in decreasing the number of ADRs in this facility.

This study is relevant to any facility with psychiatric patients, but data from this study may not be generalized to other psychiatric hospitals due to patient population, formulary considerations, and the academic nature of this hospital. Currently, this hospital's population is adults who are chronically ill; the 4-year time period of this study also includes data from a behavioral emergency room and acute care units that are no longer part of this facility. Due to the academic nature of this hospital, psychiatry residents in training frequently rotate through these units and their unfamiliarity with patients and level of training may play a role in prescribing habits. This study relied on data from spontaneous reports of ADRs and active pharmacist surveillance for ADRs. Even though organized spontaneous reporting has been shown to be a valid tool for assessing ADRs,[1] there are still concerns about underreporting, and ADRs that do not have laboratory or biological markers may not be easily identified upon pharmacist review.

Targeting high-risk medications may contribute to lowering the rates of pADRs in this population. The pharmacy department has begun implementing strategies aimed at decreasing ADRs associated with divalproex sodium and lithium. The results of the current study were presented to hospital staff at grand rounds, with emphasis on areas for improvement, such as increasing monitoring and education for psychiatry residents. Lithium drug interactions and proper monitoring of all psychotropic medications will be heavily emphasized during the pharmacist-taught pharmacology lecture series given to resident physicians. Other projects include development of a quick reference guide for monitoring parameters for mood stabilizers and atypical antipsychotics and a medication use evaluation regarding adherence to monitoring for divalproex sodium. As a result of the clozapine ADR leading to bowel obstruction and surgery, nursing is now required to ask patients about constipation with each dose of clozapine, docusate has been added to the clozapine titration protocol as a standing order, and pharmacists regularly check to ensure that patients are having regular bowel movements. Lifestyle measures to prevent constipation are indicated for every patient on clozapine, but they are not always feasible in an inpatient psychiatric setting. As a preventive measure, docusate was chosen due to its relatively benign side-effect profile, lack of drug interactions, and affordable cost.

CONCLUSION

In this extended-care, academic, state psychiatric hospital, mood stabilizers (including antiepileptics used as mood stabilizers), second-generation antipsychotics, and first-generation antipsychotics were the most common causes of ADRs. Preventable ADRs were common, with an occurrence rate of 29.7%, and almost half of all pADRs were associated with a mood stabilizer (lithium or divalproex sodium). Preventable ADRs were most often caused by drug–drug interactions and toxic serum concentrations. Pharmacists commonly made interventions to prevent ADRs, especially in regard to the drug–drug interaction between lithium and nonsteroidal anti-inflammatory drugs.

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