

## Utilization of antipsychotic therapeutic drug monitoring at a state psychiatric hospital

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### Abstract

**Introduction:** This study assesses the utilization of antipsychotic therapeutic drug monitoring (TDM) and describes characteristics of appropriate and inappropriate TDM at a state psychiatric hospital.

**Methods:** A retrospective, descriptive review was conducted for antipsychotic TDM completed between December 1, 2009, and June 30, 2011, at a 65-bed adult inpatient extended-care and forensic state psychiatric hospital.

**Results:** One hundred thirty-three ( $n = 133$ ) antipsychotic serum levels were collected from 44 patients during the study period. Sixty-nine percent (69%) of the TDM were deemed inappropriate, 28% were appropriate, and 3% could not be designated appropriate or inappropriate owing to the lack of information regarding steady-state conditions. The primary reason for inappropriate TDM was lack of documentation with regard to the indication for TDM ( $n = 79$ , 59.3%), the intervention following laboratory analysis ( $n = 88$ , 66%), or both. Appropriate TDM was associated with a lower laboratory cost for antipsychotic serum level ( $\$48.98 \pm \$53.49$  versus  $\$72.06 \pm \$51.02$ ,  $P < .05$ ), lower daily cost of scheduled psychiatric medications ( $\$17.72 \pm \$23.03$  versus  $\$32.26 \pm \$31.05$ ,  $P < .05$ ), lower daily cost of total medications ( $\$19.28 \pm \$24.91$  versus  $\$33.82 \pm \$31.03$ ,  $P < .05$ ), fewer scheduled psychiatric medications ( $2.95 \pm 1.90$  versus  $4.04 \pm 2.19$ ,  $P < .01$ ), and fewer total scheduled medications ( $5.95 \pm 3.60$  versus  $7.60 \pm 3.29$ ,  $P < .05$ ). Inappropriate TDM led to approximately \$6,753 in avoidable laboratory costs over a 20-month period.

**Discussion:** Therapeutic drug monitoring is a complex process with many points at which errors may occur. The majority of antipsychotic levels at this state psychiatric hospital were not documented in a way that was clinically useful. Inappropriate TDM was associated with increased laboratory and medication costs.

**Keywords:** therapeutic drug monitoring, antipsychotics, serum levels

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## Introduction

Therapeutic drug monitoring (TDM) is the clinical practice of measuring medication serum levels in order to optimize a patient's drug therapy regimen. In psychiatry, TDM has been used to optimize medication therapy with antidepressants, mood stabilizers, and antipsychotics. Therapeutic drug monitoring for antipsychotics is an area of interest for several reasons: (1) Some studies suggest that antipsychotic serum levels may be correlated with clinical response; (2) Antipsychotics have a delayed onset of action; (3) There is considerable individual variability in antipsychotic metabolism; and (4) It is difficult to detect early toxicity with antipsychotic therapy.<sup>1</sup> Additionally, TDM may also be indicated to confirm nonadherence (overt or surreptitious [ie, cheeking]), evaluate lack of clinical response, investigate suspected drug interactions, verify known pharmacokinetic interactions, or examine the impact of pharmacokinetically relevant comorbidities.<sup>2-4</sup>

Currently, there are varying levels of recommendation with regard to the clinical usefulness of antipsychotic serum levels. One expert consensus panel strongly recommends TDM for clozapine, fluphenazine, haloperidol, olanzapine, perphenazine, and thioridazine.<sup>3</sup> The recommendation is founded on controlled clinical trials, which have demonstrated advantageous clinical effects, including therapeutic levels, levels associated with toxicities, or both. Yet, treatment guidelines from the American Psychiatric Association, the Schizophrenia Patient Outcomes Research Team, and the National Institute for Health and Clinical Excellence have not made recommendations regarding use of TDM for antipsychotics (with the exception of clozapine).<sup>5-7</sup> Thus, routine implementation of TDM for antipsychotics remains a matter of debate. The clinical situation and the specific medication must be taken into consideration before TDM is executed.

Therapeutic drug monitoring is a complex process involving 6 essential steps: (1) Identifying a specific indication for TDM; (2) Collecting the blood sample; (3) Processing the sample in the laboratory; (4) Reporting the results; (5) Evaluating the results; and (6) Optimizing therapy.<sup>2,3</sup> Given the complexity of the process, there are many points for errors to occur. For example, the blood sample could have been collected at an inappropriate time (ie, medication not at steady state or a peak rather than trough level was obtained), the blood sample could have been processed incorrectly, or there might have been a misinterpretation of the serum level given the patient's clinical status; the end result of which could lead to inappropriate changes in medication therapy and potential negative patient outcomes. This point is highlighted in a prospective investigation of TDM of tricyclic antidepressants (TCAs), which revealed that a significant number of

dose adjustments based on TCA levels were inappropriate.<sup>8,9</sup>

Regardless of differing views of the clinical utility of TDM for antipsychotics, it was noted that at this adult inpatient psychiatric hospital, antipsychotic levels appeared to be ordered on a relatively regular basis for patients on the extended-care and forensic units. Currently, a paucity of data exists regarding the use of TDM for antipsychotics.<sup>2,3</sup> Therapeutic drug monitoring is an intriguing endeavor given the pharmacokinetics and possibility of adverse reactions associated with some of the antipsychotic agents; however, a laboratory result that does not lead to optimization of medication therapy is expensive and ineffective. The objective of this study was to assess the utilization of TDM for antipsychotics and to describe the characteristics of appropriate and inappropriate TDM at a state psychiatric hospital. The primary outcome was the percentage of antipsychotic serum levels that met criteria for appropriate TDM. Secondary outcomes included the percentage of inappropriate TDM at each step in the TDM process; potential cost savings if inappropriate TDM had been avoided; daily medication cost per patient; total number of medications per patient; and presence of antipsychotic polypharmacy in patients with appropriate TDM compared with inappropriate TDM.

## Methods

### Design

Approval for human subjects research was received from the institutional review board at the University of Missouri at Kansas City. In this retrospective, descriptive review of antipsychotic TDM, patients were included in the study if they had an antipsychotic serum level drawn between December 1, 2009, and June 30, 2011. The patient list was created by querying eLabCorp® (a secure Web-based laboratory-result retrieval system, eLabCorp®, Burlington, NC). Patients were excluded if they were discharged from the facility before the result of the antipsychotic level was communicated to the treatment team via printout or was available online on eLabCorp®.

To evaluate if TDM was appropriate, specific data were collected from each step of the TDM process for every antipsychotic serum level drawn (Table 1). When gathering data on indication for TDM, clinical status, and treatment optimization, the patient's medical record (specifically, orders and progress notes dated within a 2-week window before and after the result of the antipsychotic serum level) was examined; this allowed for the TDM process to be completed over a 4-week period. Supplemental data not found in eLabCorp® or the patient's medical record were collected from the online pharmaceutical pricing

**TABLE 1:** Specific data collected from each step of the therapeutic drug monitoring process for antipsychotic serum levels

Step in the TDM Process	Data Collected
Indication (select one)	<ul style="list-style-type: none"> <li>• Suspected nonadherence</li> <li>• Lack of clinical response, or insufficient response even if dose considered adequate</li> <li>• Suspected drug interaction</li> <li>• Combination treatment with a drug known for its pharmacokinetic interaction</li> <li>• Recurrence of symptoms despite good adherence and adequate dose</li> <li>• Pharmacokinetically relevant comorbidities (hepatic or renal insufficiency)</li> <li>• Validation that serum level is therapeutic</li> <li>• No indication</li> </ul>
Blood sample collection	<ul style="list-style-type: none"> <li>• Date that antipsychotic was initiated</li> <li>• Date and time that the last dose of antipsychotic was administered prior to blood sample collection</li> <li>• Date and time that the blood sample was collected</li> </ul>
Evaluation of results (yes/no)	Consideration of patient's clinical state (ie, presence or absence in progress note)
Treatment optimization (select one)	<ul style="list-style-type: none"> <li>• Change in dose</li> <li>• Change in dosage form</li> <li>• Cessation of drug</li> <li>• Change in concomitant medication</li> <li>• Discussion of results with patient (eg, adherence, safety)</li> <li>• Pharmacogenetic testing</li> <li>• Order written for nursing supervision and mouth-check</li> <li>• Validation that serum level is therapeutic</li> <li>• Other</li> <li>• No intervention</li> </ul>

TDM = therapeutic drug monitoring.

catalog for pharmaceutical wholesaler Morris & Dickson Co, LLC (Shreveport, LA), and from the state psychiatric hospital's pharmacy computer software (Quadramed®, QuadraMed Corporation, Reston, VA).

## Costs

Data regarding laboratory and medication costs were collected from LabCorp® and from Morris & Dickson Co, LLC, respectively. Laboratory costs for antipsychotic serum levels were as follows: aripiprazole, \$184.25; clozapine, \$20.28; haloperidol, \$16.00; fluphenazine, \$92.00; olanzapine, \$124.00; quetiapine, \$154.50; risperidone, \$109.00; and ziprasidone, \$107.00; the cost of the phlebotomist collecting the sample from the patient was not included in the laboratory cost. The potential cost savings if inappropriate TDM had been avoided was calculated by totaling the laboratory cost of all inappropriate TDM. Daily medication costs were calculated based on each patient's scheduled medications; the cost of as-needed medications was not included.

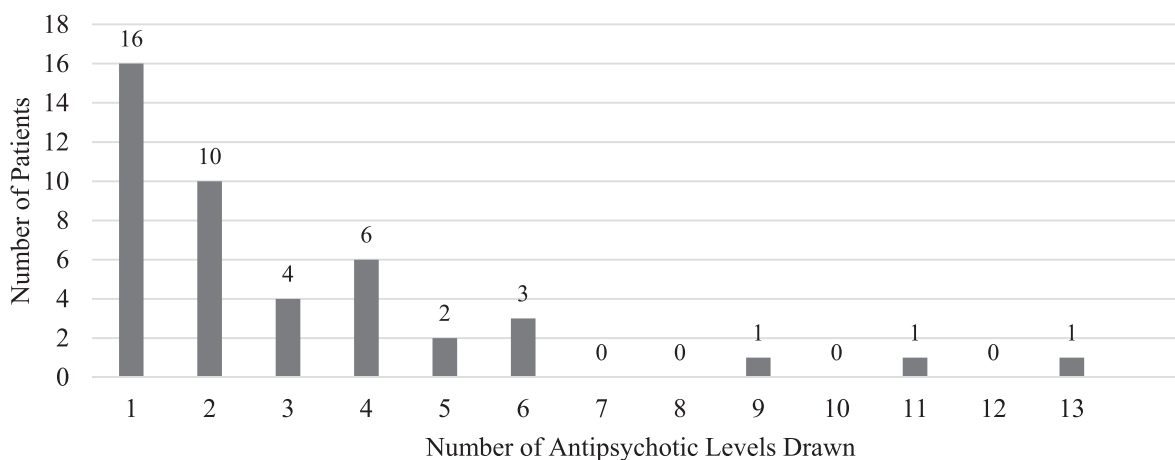
## Definition of Appropriate TDM

For the purpose of this study, the following definition for *appropriate TDM* was used. In order to be considered

appropriate, the TDM of an antipsychotic serum level had to meet all 4 of the following criteria: (1) A specific indication for TDM was documented in the medical record; (2) The blood sample was collected at steady state; (3) A statement regarding the patient's clinical status was present in the medical record; and (4) Subsequent treatment optimization occurred. If any of the above criteria was not fulfilled, the TDM was considered inappropriate. However, if the indication was for suspected nonadherence, then the blood sample did not have to be collected at steady state. This study assumed that a validated method was used to process the blood sample and that the result was communicated to the treatment team via printout or was available online at eLabCorp® in timely manner. The definition of *appropriate TDM* was created for the purpose of this study and was based upon best practices and recommendations by an expert consensus panel.<sup>3</sup> Additionally, the definition was approved by the hospital's Pharmacy and Therapeutics Committee.

## Analysis

Chi-square test and analysis of variance (ANOVA) were used to evaluate any differences in indication for TDM, the steps in which inappropriate utilization of TDM



**FIGURE 1:** Number of antipsychotic levels drawn per patient (n = 44)

occurred, and the action or intervention completed following prescriber notification of the antipsychotic serum level. Student *t* test was used to evaluate differences in the mean daily medication cost, the mean total number of scheduled medications per patient, and the presence of antipsychotic medication polypharmacy between patients with appropriate antipsychotic TDM compared with inappropriate antipsychotic TDM.

## Results

A total of 44 patients had 133 antipsychotic serum levels collected during the study period. Thirteen of the patients (30%) were female, and 31 (70%) were male. The average age was 38.8 years (range, 18-73 years; SD, 14.4). Patients had a variety of primary psychiatric diagnoses: schizophrenia (n = 23); schizoaffective disorder (n = 13); psychosis, not otherwise specified (n = 3); impulse control disorder (n = 3); dementia (n = 1); and posttraumatic stress disorder (n = 1).<sup>10</sup> The median number of antipsychotic serum levels drawn per patient was 2 (range, 1-13) (Figure 1). Twenty-five different prescribers ordered antipsychotic serum levels; 8 prescribers were attending psychiatrists, and 17 were psychiatric residents. The median number of antipsychotic serum levels ordered per prescriber was 2 (range, 1-34). Antipsychotic serum levels were drawn for clozapine (n = 51, 38.3%), risperidone (n = 26, 19.6%), haloperidol (n = 22, 16.5%), olanzapine (n = 19, 14.3%), fluphenazine (n = 9, 6.8%), and aripiprazole (n = 6, 4.5%).

Seventy-nine serum levels (n = 79, 59.3%) had no documented indication for TDM (Table 2). Documented indications for antipsychotic TDM included validation of therapeutic level (n = 29, 21.8%), suspected nonadherence (n = 13, 9.8%), lack of clinical response despite adequate dose (n = 5, 3.8%), recurrence of symptoms despite good adherence and adequate dose (n = 4, 3%), and evaluation

of a known drug interaction (n = 3, 2.3%). No antipsychotic TDM was performed to evaluate the effect of pharmacokinetically relevant comorbidities.

In terms of timing of blood sample collection, the threshold for determining steady-state status was based on information from the antipsychotic's package insert or other published literature regarding the pharmacokinetics of the antipsychotic. Eighty-nine of 133 antipsychotic levels (n = 89, 66.9%) were collected at steady state, and 25 levels (18.8%) were not at steady state at the time of collection. Steady-state status was not able to be determined for 19 antipsychotic levels (14.3%), either because the level was drawn upon admission to the hospital (n = 12) or because the patient received the long-acting injectable formulation of the antipsychotic, which was continued upon admission (n = 7).

The result of the antipsychotic serum level was communicated to the prescriber and the treatment team, and 88 of the levels (66%) had no documentation describing the need (or lack of need) for intervention or treatment optimization. Documented interventions, treatment optimization strategies, or both, included validation of therapeutic level (n = 21, 15.8%), change in dose (n = 7, 5.3%), cessation of the drug (n = 7, 5.3%), change in dosage form (n = 4, 3%), discussion of the results with the patient (n = 4, 3%), change in concomitant medication (n = 1, 0.8%), and order written for mouth-check following administration of the antipsychotic (n = 1, 0.8%). Pharmacogenetic testing was not ordered in response to the results of any of the antipsychotic serum levels.

Ninety-two of 133 of the antipsychotic TDM (n = 92, 69%) were deemed inappropriate, 37 (28%) were appropriate, and 4 of the TDM (3%) could not be designated appropriate or inappropriate because of the lack of information regarding steady-state status. A majority of levels were inappropriate for more than one reason (eg,

**TABLE 2: Documentation of antipsychotic therapeutic drug monitoring by patient**

Patient ID	Number of Antipsychotic Serum Levels With Documentation of an Indication, n (%)	Total Number of Antipsychotic Levels
1	0 (0%)	1
2	1 (100%)	1
3	0 (0%)	2
4	1 (50%)	2
5	2 (50%)	4
6	1 (100%)	1
7	2 (50%)	4
8	0 (0%)	1
9	1 (25%)	4
10	1 (100%)	1
11	0 (0%)	1
12	1 (9%)	11
13	4 (31%)	13
14	0 (0%)	2
15	0 (0%)	1
16	1 (100%)	1
17	4 (67%)	6
18	0 (0%)	3
19	1 (100%)	1
20	1 (25%)	4
21	0 (0%)	2
22	1 (100%)	1
23	2 (100%)	2
24	1 (25%)	4
25	1 (100%)	1
26	0 (0%)	1
27	0 (0%)	4
28	3 (100%)	3
29	6 (100%)	6
30	0 (0%)	2
31	0 (0%)	1
32	3 (33%)	9
33	2 (67%)	3
34	2 (33%)	6
35	4 (80%)	5
36	0 (0%)	1
37	2 (100%)	2
38	2 (40%)	5
39	0 (0%)	1
40	0 (0%)	1
41	1 (50%)	2
42	0 (0%)	2
43	1 (33%)	3
44	2 (100%)	2

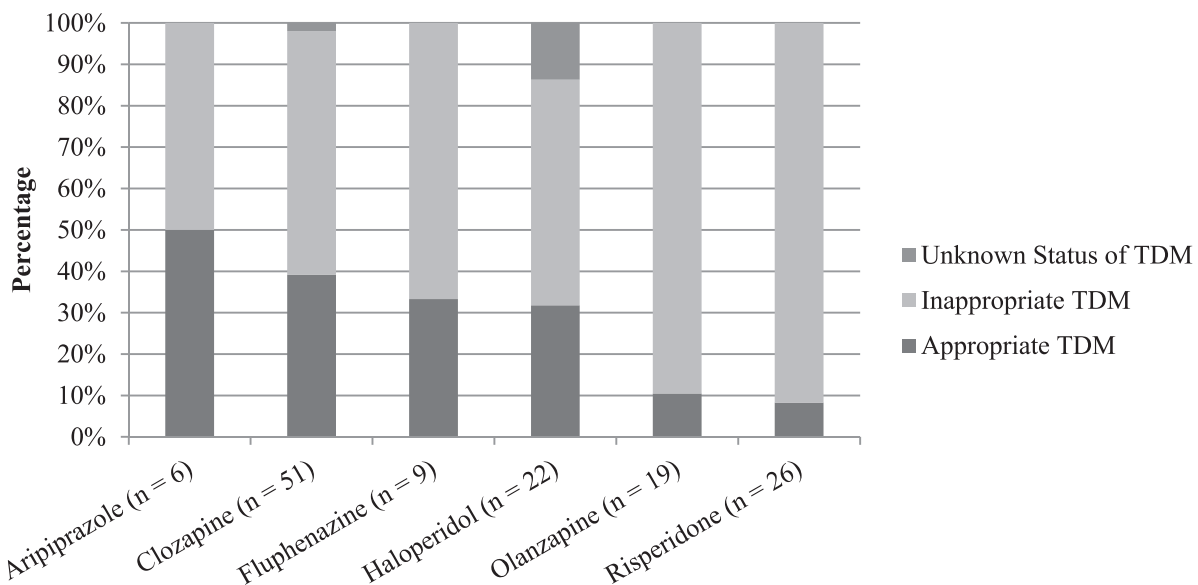
no indication and no documented intervention). Aripiprazole and clozapine had the highest percentage of appropriate TDM (Figure 2). Attending psychiatrists had a higher rate of appropriate TDM compared with psychiatric residents (32% [28/37] versus 20% [9/46]). Appropriate TDM was associated with a lower laboratory cost for antipsychotic serum level ( $\$48.98 \pm \$53.49$  versus  $\$72.06 \pm \$51.02$ ,  $P < .05$ ), lower daily cost of scheduled psychiatric medications ( $\$17.72 \pm \$23.03$  versus  $\$32.26 \pm \$31.05$ ,  $P < .05$ ), lower daily cost of total medications ( $\$19.28 \pm \$24.91$  versus  $\$33.82 \pm \$31.03$ ,  $P < .05$ ), fewer scheduled psychiatric medications ( $2.95 \pm 1.90$  versus  $4.04 \pm 2.19$ ,  $P < .01$ ), and fewer total scheduled medications ( $5.95 \pm 3.60$  versus  $7.60 \pm 3.29$ ,  $P < .05$ ). Inappropriate TDM led to approximately \$6,753 in avoidable laboratory costs over a 20-month period. No significant difference was found between the appropriate and inappropriate groups for the number of nonpsychiatric medications ( $3.00 \pm 2.58$  versus  $3.55 \pm 2.59$ , respectively,  $P > .05$ ), the daily cost of nonpsychiatric medications ( $\$1.57 \pm \$4.15$  versus  $\$1.57 \pm \$3.40$ , respectively,  $P > .05$ ), and the number of antipsychotic medications ( $1.43 \pm 0.69$  versus  $1.65 \pm 0.82$ , respectively,  $P > .05$ ).

## Discussion

A majority of the antipsychotic serum levels drawn during the study period did not meet criteria for appropriate TDM. The primary reason for inappropriate TDM was lack of documentation with regard to the indication for TDM ( $n = 79$ , 59.3%) and/or the intervention/treatment optimization following antipsychotic laboratory analysis ( $n = 88$ , 66%). Clozapine serum levels were drawn most frequently and were one of the least expensive labs to obtain. There was also a relatively high percentage of appropriate TDM for clozapine. Not surprising, attending psychiatrists had a higher rate of appropriate antipsychotic TDM compared with the psychiatric residents who are still in training. Patients with inappropriate antipsychotic TDM had significantly more scheduled psychiatric medications, perhaps indicating a more treatment-resistant population.

This study has several important limitations. The most influential limitation was the study design (ie, retrospective chart review). Therefore, it was limited by what was documented in the medical record. The prescriber may have considered each step of the TDM process yet may not have thoroughly documented their actions. Owing to prescriber and patient turnover, attempts to reconcile discrepancies in antipsychotic TDM execution and documentation were not made. Several other limitations exist as well. The pharmacist's role in the TDM process for antipsychotics at the hospital was not known. Although a





**FIGURE 2:** Percentage of appropriate antipsychotic therapeutic drug monitoring (TDM) according to type of antipsychotic level

pharmacist is assigned to each treatment team and is an active member in the patient's care, a reliable method currently does not exist for detecting if a pharmacist was consulted regarding TDM of antipsychotics. Documentation of the pharmacist's role in TDM may help to streamline the TDM process in the future. Additionally, there may have been inaccuracies in executing appropriate TDM orders. Prescribers may have ordered appropriate monitoring within the correct time frame, but execution depends on several factors. Variations in the timing of nursing staff carrying out the laboratory orders or of laboratory staff drawing the blood samples may occur. Also, patients may choose to refuse blood draws during the specific monitoring time period, or even altogether. Last, this study took place at a small adult inpatient state psychiatric facility, which could make the results of this study difficult to apply in facilities with different policies and patient populations.

Given the results of this study, the hospital considered several options for increasing the percentage of appropriate TDM for antipsychotics. The first strategy was to implement educational interventions. A formal presentation outlining the TDM process, intricacies in TDM between different antipsychotics, and appropriate documentation was delivered by a pharmacist to the hospital staff in a Grand Rounds setting; attendance at Grand Rounds is required for psychiatrists and residents. An update of the facility policies and procedures, including creation of an order set or menu for antipsychotic TDM, was discussed but not implemented as the Grand Rounds' presentation was well received based on evaluation and written feedback of the presentation by the medical staff. Furthermore, the pharmacists assigned to each unit have

observed a decrease in the number of antipsychotic serum levels ordered in the months following the presentation; formal reevaluation of antipsychotic TDM was not completed.

Therapeutic drug monitoring is a complex process with many points at which errors may occur. The majority of antipsychotic levels at this state psychiatric hospital were not documented in a way that was clinically useful. Inappropriate TDM was associated with increased laboratory and medication costs. In the future, this may be an opportunity for increased involvement of pharmacy services.

## Acknowledgments

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