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Best practices for documentation of psychotropic drug-drug interactions in an adult psychiatric clinic

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Abstract

Introduction: Psychotropic drug-drug interactions (DDIs) contribute to adverse drug events, but many go undetected or unmanaged. Thorough documentation of potential DDIs can improve patient safety. The primary objective of this study is to determine the quality of and factors associated with documentation of DDIs in an adult psychiatric clinic run by postgraduate year 3 psychiatry residents (PGY3s).

Methods: A list of high-alert psychotropic medications was identified by consulting primary literature on DDIs and clinic records. Charts of patients prescribed these medications by PGY3 residents from July 2021 to March 2022 were reviewed to detect potential DDIs and assess documentation. Chart documentation of DDIs was noted as none, partial, or complete.

Results: Chart review identified 146 DDIs among 129 patients. Among the 146 DDIs, 65% were not documented, 24% were partially documented, and 11% had complete documentation. The percentage of pharmacodynamic interactions documented was 68.6% with 35.3% of pharmacokinetic interactions documented. Factors associated with partial or complete documentation included diagnosis of psychotic disorder ($p = .003$), treatment with clozapine ($p = .02$), treatment with benzodiazepine-receptor agonist ($p < .01$), and assumption of care during July ($p = .04$). Factors associated with no documentation include diagnosis of "other (primarily impulse control disorder)" ($p < .01$) and taking an enzyme-inhibiting antidepressant ($p < .01$).

Discussion: Investigators propose best practices for psychotropic DDI documentation: (1) description and potential outcome of DDI, (2) monitoring and management, (3) Patient education on DDI, and (4) patient response to DDI education. Strategies to improve DDI documentation quality include targeted provider education, incentives, and electronic medical record "DDI smart phrases."

Keywords: drug interactions, patient safety, documentation, quality improvement, psychotropic

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Introduction

Adverse drug events (ADEs) are significant concerns for patients living with psychiatric conditions and are often caused by drug-drug interactions (DDIs).[1] These DDIs commonly involve psychotropics and go under-recognized and under-reported.[2-5] The 2020 American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia specifically warns about the potential for DDIs between antipsychotics (APs) and other prescribed medications.[6]

Management of DDIs is especially pertinent in psychiatry as many patients are prescribed multiple psychotropics. A national analysis of 13 079 adult outpatient psychiatry visits found approximately half of patients were prescribed at least 2 psychotropics, and a third of patients were prescribed 3 or more.[7] Further, many psychotropics are modulators of cytochrome P450 (CYP450) enzymes or have overlapping pharmacodynamic (PD) effects, increasing the potential for DDIs and subsequent ADEs. One study found that those prescribed risperidone were significantly more likely to discontinue treatment due to an ADE if coprescribed a CYP450 inhibitor.[8]

Several barriers exist that prevent effective psychotropic DDI documentation, including discrepancies between commercially available drug-interaction databases.[9,10] In addition, insufficiencies associated with computerized interaction alert systems can overwhelm prescribers with excessive alerts, leading to "alert fatigue," which decreases attentiveness to potential DDIs.[11,12] Though pharmacists are indispensable in preventing DDI-related ADEs, an upstream approach is to equip prescribers and patients with the skills necessary to prevent such events.[13-15] Although some educational interventions demonstrate success in reducing prescribing associated with DDIs, others fail to change prescribing practices.[16-18] Moreover, the complex nature of psychiatric diagnoses often dictates the need for multiple psychotropics, so alternative strategies must be developed to improve patient safety.[19]

Proper documentation of potential DDIs can prevent ADEs and better inform pharmacotherapy decisions.[20,21] Quality improvement initiatives have been successful in improving several aspects of medical record documentation, including psychotropic side effects and general adverse drug reactions.[22-26] Nonetheless, there is a dearth of literature describing the behaviors of providers related to patient education on psychotropic DDIs. Psychiatric literature lacks recommendations on best practices for documenting psychotropic DDIs and associated patient education and interventions in the medical record. Further, there are no studies that evaluate factors associated with the quality of psychotropic DDI documentation.

This study was conducted at a clinic staffed by 10 PGY3 psychiatry residents, 6 psychiatrist attendings, a board-certified psychiatric pharmacist (BCPP), and a PGY2 psychiatric pharmacy resident, and they serve approximately 1100 patients annually via medication management and psychotherapeutic services.

The psychiatrist clinic director engaged the PGY2 psychiatric pharmacy resident and BCPP to conduct a quality improvement research project with the following specific aims:

1. Identify psychiatric medication combinations with potential for significant DDIs in a caseload of approximately 1100 adults treated for psychiatric diagnoses at an academic medical center.
2. Assess documentation of DDIs, including description and potential outcome, management, patient education, and patient informed consent in the medical record.
3. Determine factors associated with DDI documentation quality.

This quality improvement research aims to bring attention to psychotropic DDIs and encourage health systems to develop comprehensive DDI documentation policies. The authors recommend the following 4 components of DDI documentation: (1) description and potential outcome of DDI, (2) monitoring and management, (3) patient education on DDI, and (4) patient response to DDI education.

Methods

This was an institutional review board–exempt, retrospective study conducted at a resident-run adult psychiatric clinic within an academic medical center. Chart reviews were performed to determine current DDI documentation and identify factors that impact documentation quality. To achieve this end, a list of 10 high-alert psychotropics or psychotropic classes was developed based on primary literature identifying psychotropics at greatest risk of ADEs and consideration of pharmacokinetic (PK) and PD principles as they apply to psychotropics.[27-29] The high-alert medication list was tailored to the prescribing patterns in the clinic. Of note, the decision was made to exclude lithium as a high-alert medication as only 2 patients were prescribed lithium in the entire clinic. In addition, a category of multiple concomitant APs not undergoing cross-titration was added to the high-alert medication list given the Joint Commission National Quality Measures regarding appropriate use of multiple routine APs.[30] The high-alert medication list is included in Table 1.

An electronic report of medications prescribed by PGY3 psychiatry residents from July 1, 2021, to October 28, 2022, was generated. The report was screened for high-alert medications, and each patient receiving a high-alert medication was evaluated for the presence of a known or established DDI. Screened interactions were limited to psychotropic combinations given that these can be adjusted or changed by study clinic providers. Additive PD effects of interest were determined by study investigators and included sedation, dizziness/hypotension, hypertension, tachycardia, anticholinergic effects, extrapyramidal side effects, and increased risk of seizures. The decision to attribute a PD effect to a medication or medication class was based on the severity of outcome (ie, seizures) or high ($>$ 10%) incidence reported from clinical trials (ie, sedation

TABLE 1: Medication level factors associated with quality of documentation of DDIs

Factor	Total Number of DDIs, *n* (%) (*n* = 146)	Complete or Partial Documentation, *n* (%) (= 51)	No Documentation, *n* (%) (= 95)	*P* Value
High-alert medication or medication class				
Clozapine	12 (8.2)	8 (15.7)	4 (4.2)	.02[g]
Benzodiazepine receptor agonists[a]	38 (26.0)	21 (41.2)	17 (17.9)	<.1[g]
Psychostimulants[b] and atomoxetine	14 (9.6)	2 (3.9)	12 (12.6)	.09
Lamotrigine	11 (7.5)	3 (5.9)	8 (8.4)	.75
Valproate	9 (6.2)	1 (2.0)	8 (8.4)	.16
Enzyme-inhibiting antidepressants[c]	71 (48.6)	17 (33.3)	54 (56.8)	< .01[g]
Inducer antiseizure medications[d]	4 (2.7)	0 (0.0)	4 (4.2)	.30
Tricyclic antidepressants[e]	12 (8.2)	3 (5.9)	9 (9.5)	.54
Propranolol	11 (7.5)	3 (5.9)	8 (8.4)	.75
2 or more APs not undergoing titration	11 (7.5)	7 (13.7)	4 (4.2)	.05
Number of medications				
Involved in DDI				.26
2	111 (76.0)	36 (70.6)	75 (79.0)	
3 to 5	35 (24.0)	15 (29.4)	20 (21.1)	
Prescribed by resident provider	3.22 (± 1.1)	3.14 (± 1.2)	3.26 (± 1.0)	.50
Prescribed by all providers	6.73 (± 4.0)	7.25 (± 3.9)	6.44 (± 4.0)	.24
Type of interaction				
Pharmacokinetic	72 (49.3)	18 (35.3)	54 (56.8)	.01[g]
UGT inhibition	1 (0.7)	0 (0.0)	1 (1.1)	1.00
Increased free valproate level (protein binding displacement)	1 (0.7)	1 (2.0)	0 (0.0)	.35
CYP inhibition	70 (48.0)	17 (33.3)	53 (55.8)	.01[g]
Pharmacodynamic	79 (54.1)	35 (68.6)	44 (46.3)	.01[g]
Additive AP side effects including EPS from 2 or more APs[f]	11 (7.5)	7 (13.7)	4 (4.2)	.05
Non-AP additive side effects Sedation	43 (29.5)	18 (35.3)	25 (26.3)	.26
Dizziness/hypotension	43 (29.5)	17 (33.3)	26 (27.4)	.45
Seizures	5 (3.4)	2 (3.9)	3 (3.2)	1.00
Tachycardia/hypertension	7 (4.8)	2 (3.9)	5 (5.3)	1.00
Anticholinergic effects	4 (2.7)	0 (0.0)	4 (4.2)	.30
Treatment of clozapine-induced tachycardia	6 (4.1)	5 (9.8)	1 (1.1)	.02[g]
Date of initiation or continuation of DDI				.04[g]
July 1 to 31, 2021	66 (45.2)	29 (56.9)	37 (39.0)	
August 1 to October 28, 2021	80 (54.8)	22 (43.1)	58 (61.1)	

AP = antipsychotic; CYP = cytochrome P; DDI = drug-drug interaction; EPS = extrapyramidal side effects; UGT = uridine glucuronyl transferases.

Data are presented as count (column percentage) or mean (±SD). The sum of items in "High-alert medication or medication class" and "Type of interaction" do not equal the total number of DDIs as some interactions include multiple high-alert medications or are characterized by multiple types of interactions. Extrapyramidal side effects include pseudoparkinsonism, akathisia, dystonia, and tardive dyskinesia.

[a]Alprazolam, clonazepam, lorazepam, temazepam, zolpidem.

[b]Dextroamphetamine, mixed amphetamine salts, lisdexamfetamine.

[c]Bupropion, duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline.

[d]Darbamazepine, oxcarbazepine.

[e]Amitriptyline, doxepin, nortriptyline.

[f]Category did not include clozapine; no subjects on clozapine with a concomitant AP.

[g]*P* value < .05 indicates statistical significance.

TABLE 2: Proposed best practices for psychotropic DDI documentation

Documentation Component	Examples of Partial Documentation	Examples of Complete Documentation	Recommended Standard Verbiage or "Smart Phrase Example"
1. DDI description and potential outcome	"Risk of side effects increased with medication A + medication B combination"	"Medication A is a strong CYP2D6 inhibitor, medication B is a CYP2D6 substrate. Coadministration may increase medication B levels with increased risk of adverse effects"	There is a potential DDI between ___ and ___ due to [mechanism] that could result in [outcome].
2. Monitoring and management of DDI	"Drug-drug interactions reviewed" "Advised close f/u."	"Only starting medication A at 2 mg, plasma levels will likely be higher given CYP2D6 enzyme inhibition by medication B."	Will minimize risk by [management strategy] and/or will monitor for ___.
3. Patient education on DDI	"Benefits and risks explained. Drug information pamphlet given"	"Risks/benefits/alternatives to meds listed below discussed, including but not limited to risk of seizures on medication A + medication B"	Provided verbal/ written education on potential DDI between _____ and _____ and instructed patient to [monitor/report/ management].
4. Patient response to education and consent to treatment[a]	"Patient acknowledged information regarding treatment. Patient expressed willingness to consider proposed treatment plan"	"Patient verbalized understanding and agreed to increase medication A dose."	Patient verbalized understanding of information provided including DDI education and consented to _____.
	"Pt appears to have understanding and agrees with above interventions"	"Patient consented to continue taking medication A and medication B; completed medication consent and treatment plan"	

DDI = drug-drug interaction.

[a]Documentation for informed consent was classified as partial if the verbiage was vague and did not convey that client verbalized understanding and agreed to the treatment plan.

from BZRA or clozapine). Pharmacokinetic interactions included mild-to-severe metabolic inhibition/induction or protein-binding displacement resulting in potential for increased or decreased blood levels of a psychotropic as defined by labeling or primary literature. Interactions involving p-glycoprotein were not assessed. One patient could have multiple PD or PK interactions tallied separately and displayed in Table 1.

Screened patients were excluded if psychotropic medications were not prescribed concomitantly upon chart review. Resident chart documentation from July 1, 2021, to March 31, 2022, was examined by the primary researcher and research assistant for verbiage related to specific DDI documentation components, which can be found in Table 2. The clinic has a standardized outpatient psychiatry follow-up note template. Sections pertinent to DDI documentation, including medication list, medication reconciliation, intervention, and patient response, were assessed by researchers. The date of the DDI documentation was recorded to determine the effect of time in training on DDI quality.

Drug interaction documentation was classified as none, partial, or complete for each interaction. Partial documentation failed to meet expectations for all 4 components of recommended documentation in Table 2. Examples of partial documentation included not describing the mechanism or potential outcome of the DDI, not specifying which medications were involved in the DDI, not documenting provision of patient education, or not documenting informed consent to treatment after the DDI was explained to the patient. Investigators combined the partial and complete DDI documentation for statistical comparison given the low rate of complete documentation.

Descriptive statistics were used to categorize patient characteristics, DDI, and documentation quality. Comparisons were performed between partial/complete and no documentation groups. (Tables 1 and 3) Chi-square or Fisher exact tests were performed for categorical variables, and *t* or Wilcoxon Mann-Whitney tests (nonparametric) were applied to continuous variables to determine the group difference. All analyses were conducted using SAS version 9.4 (Cary, North Carolina).

Results

After screening for interacting psychotropics and other inclusion criteria, a total of 146 DDIs were identified among

TABLE 3: Patient-level factors associated with quality of DDI documentation

Factor	Total Number of DDIs ($n = 146$)	Complete or Partial Documentation ($n = 51$)	No Documentation ($n = 95$)	*P* Value
Patient characteristics				
Gender (female), *n* (%)	78 (53.4)	25 (49.0)	53 (55.8)	.43
Age, average ± SD	43.1 ± 13.9	44.9 ± 14.7	42.2 ± 13.4	.27
Diagnostic category, *n* (%)				
Affective disorder	53 (36.3)	19 (37.3)	34 (35.8)	.86
Anxiety or stress-related disorder	31 (21.2)	11 (21.6)	20 (21.1)	.94
Neurodevelopmental disorder	27 (18.5)	4 (7.8)	14 (14.7)	.23
Psychotic disorder	18 (12.3)	16 (31.4)	11 (11.6)	.003[b]
Other disorder[a]	17 (11.6)	1 (2.0)	16 (16.8)	< .01[b]
Number of visits, average ± SD	5.99 ± 3.7	6.66 ± 3.1	5.64 ± 4.0	.15

DDI = drug-drug interaction.

Data are presented as count (column percentage) or mean (± SD).

[a]Includes impulse disorders ($n = 13$), personality disorders ($n = 3$), and neurocognitive disorder ($n = 1$).

[b]*P* value < .05 indicates statistical significance.

129 patients (Table 1). Thirty-seven interactions (25.3%) were defined by multiple additive PD and/or PK effects (eg, both CYP450 inhibition and additive risk of hypertension with bupropion-amphetamine salts combination). Fifty-four interactions (37.0%) involved 2 or more high-alert medications, and 35 (24.0%) interactions involved 3 or more medications (eg, additive sedation and dizziness with mirtazapine, gabapentin, and alprazolam combination) (Table 4). Patient characteristics are presented in Table 3. Patients were 43.1 years of age on average, majority female (53.4%), and primarily diagnosed with affective disorders. The average number of visits per patient in the study period was 6. Patients were prescribed an average of 3 psychotropics, and each patient's mean total number of medications was 7 including nonpsychotropics prescribed by other providers.

Regarding documentation, 95 (65.1%) DDIs were not documented, 35 (24.0%) were partially documented, and 16 (11.0%) had complete documentation. PD interactions were significantly more likely to have partial/complete documentation compared with PK interactions (68.6% versus 35.3%, $p = .01$) (Table 1). Interactions involving clozapine ($p = .02$) or benzodiazepine receptor agonists ($p < .01$) were significantly more likely to have partial or complete documentation compared with interactions involving enzyme-inhibiting antidepressants ($p < .01$), which were less likely to be documented (Table 1).

Statistical analysis revealed other factors strongly associated with likelihood of documentation, including psychotic disorders ($p = .003$), and initiation/continuation of the DDI early on in resident training (July 1 to 31, 2021; $p = .04$). Conversely, DDIs involving "other" disorders (primarily made up of impulse-control disorders; $p < .01$), and initiation/continuation of DDI later in residency year (August 1 to October 28, 2021; $p = .04$) were associated with likelihood of no documentation.

TABLE 4: Quantification of prescriptions, patients, and DDIs

Variable	Number
Prescription level	
High-alert medications prescribed by PGY3 residents July 1, 2021, to March 31, 2022, including clozapine but not other APs	621
APs prescribed by residents July 1, 2021, to March 31, 2022, excluding clozapine	348
Patient level	
Patients prescribed high-alert medications by PGY3 residents July 1, 2021, to March 31, 2022, including clozapine but not other APs	371
Patients prescribed high-alert medications involving DDIs	129 (34.8)
Patients prescribed APs by PGY3 residents July 1, 2021, to March 31, 2022, excluding clozapine	314
Patients prescribed multiple APs not undergoing cross-titration	11 (3.5)
DDI level	
DDIs involving high-alert medications	146
DDIs involving three or more medications	35 (24.0)
DDIs defined by 2 or more PD or PK effects	37 (25.3)
DDIs involving 2 or more high-alert medications	54 (37.0)

AP = antipsychotic; DDI = drug-drug interaction; PD = pharmacodynamic; PGY3 = postgraduate year 3; PK = pharmacokinetic.

Data are presented as count (column percentage)

Discussion

The results of this study present many opportunities to improve documentation of DDIs as approximately two thirds of DDIs had no documentation. Enzyme-inhibiting antidepressants represented a significant portion of the undocumented DDIs, which is likely a result of high frequency of use in the outpatient setting and routine concurrent use with CYP450 substrates. One potential reason for low DDI documentation is lower prescribing rates of antidepressants in the inpatient setting in which psychiatry residents primarily train for the first 2 years. On the contrary, clozapine and BZRAs are frequently prescribed inpatient, and residents' higher rates of documentation may represent more knowledge and experience of potential risks and severity of DDIs with these agents.

The research team developed several recommendations to provide to clinic leadership that could be implemented immediately. The research team recommends each incoming resident provider screen the provider's caseload for DDIs and complete the 4 DDI documentation components (Table 2) annually during the first patient encounter note and when drug therapy changes introduce new DDIs. These 4 components are essential to document that a DDI risk versus benefit analysis took place and ensure the patient and all providers are fully informed of potential adverse outcomes and need for monitoring to ensure safety. During chart review, a prominence of inadequate verbiage regarding DDI management, particularly regarding patient response or informed patient consent, was recorded. The free-text documentation on the standard clinic note is likely a contributing factor. Standardized documentation templates improve documentation quality and, thus, medical record "smart phrases" were created for residents to incorporate into their practice (Table 2).[31,32] There was also a lack of documentation regarding written patient education on DDIs. To remedy this, a patient education handout on DDI management with a section for the provider to describe specific DDI management strategies for the patient was created. Finally, third-year psychiatry residents participate in weekly didactic programming, which includes sessions on psychopharmacology and DDIs. These sessions are opportunities to increase provider skills in DDI management, and the research team recommends including a component of DDI management and documentation in psychopharmacology didactic sessions throughout the year. This type of education with provider incentives for evidence of improved DDI documentation can be applied to other psychiatry clinics.

These best practice recommendations for psychotropic DDI documentation were presented to the current residency class, and feedback was received via discussion and a survey that asked residents to describe how their knowledge of DDIs and documentation practices changed throughout the year. In addition, these recommendations will be presented by the BCPP and PGY2 psychiatric pharmacy resident during didactic sessions in orientation for each new class of incoming PGY3 residents.

This study has several limitations. Definitions of PD effects of psychotropics were defined by class for some medications. For example, all APs were assigned PD effects of sedation and extrapyramidal side effects even though an antipsychotic such as quetiapine is associated with relatively higher risk of sedation than ziprasidone and lower risk of extrapyramidal side effects than risperidone.[6] This strategy was employed to account for individual patient differences in the occurrence of side effects. It also helped ensure high inter-rater fidelity between the primary researcher and research assistant. Additionally, interactions between high-alert medications and nonpsychotropics were not captured. Finally, the clinical significance of DDIs and their documentation on patient safety or ADEs was not assessed in this chart review.

Conclusions

This is the first study to describe the quality of DDI documentation in an outpatient psychiatry setting. Overall, the majority of psychotropic drug interactions were not or only partially documented. Several factors significantly impacted DDI documentation quality, including the type of DDI, the psychotropics involved, and patient diagnosis. Best practices for documentation should include (1) DDI description and potential outcome, (2) DDI monitoring and management, (3) patient education on DDI, and (4) patient response and consent to treatment with DDI monitoring. Integration of a BCPP and PGY2 psychiatric pharmacy resident to an adult psychiatry clinic presents the opportunity to increase awareness of and education on psychotropic DDIs. Investigators hope this research prompts other clinics to evaluate and improve their documentation of psychotropic DDIs.

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