DETECTING DRUG–DRUG INTERACTIONS IN MEDICATION PROFILES OF PSYCHIATRIC INPATIENTS: A TWO-STAGE APPROACH

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Abstract: A two-stage evaluation methodology was developed to detect drug–drug interactions (D-DIs) of moderate and major severity in a psychiatric inpatient population. During a 3-month study period, the medication orders prescribed for 152 psychiatric inpatients in two psychiatric wards of a medical center were examined. A primary assessment of patients’ reactions due to drug interactions was carried out by physicians who were provided with pertinent drug interaction monographs. A secondary assessment was performed by a three-member committee using explicit criteria to decide which reactions were actual D-DIs. Potential moderate or major severity D-DIs were identified in 79 (52.0%) of the 152 patients. A total of 130 potential interactions were detected in 339 (63.1%) of the 537 medication profiles. Actual D-DIs were seen in two patients (1.3%) who were prescribed trazodone with chlorpromazine and doxepin with paroxetine, respectively. The discrepancy between incidences of potential and actual D-DIs suggests that the method was sensitive in the detection and prudent in the assessment of D-DIs.

Methods

Patients

This prospective study was carried out between November 1999 and January 2000 in two psychiatric wards of National Taiwan University Hospital (NTUH), a medical center in Taipei. Except for those receiving only a single medication, all patients admitted to the NTUH Department of Psychiatry during the study period were included in the study. Topical interactions in psychiatric patient populations is particularly difficult [12]. The purpose of this study was to employ a mechanistic approach to prospectively investigate the incidence of potential and clinically significant D-DIs in a psychiatric inpatient population.
agents with limited systemic absorption and amisulpiride, a drug that at the time of the study was not included in any of the four reference resources used as appraisal guidelines [13–16], were not checked for interaction potential against other drugs in the medication profiles.

**Study design**

To allow the investigators to fine-tune the study protocol and the primary care teams to become acquainted with the study procedures, a 1-month run-in period was included prior to the start of the study (October 1999). During this period, monographs of encountered drug pairs (object drug-precipitant drug) with interaction potentials of moderate or major severity were designed in accordance with references frequently used by clinicians for drug interactions [13–16]. The 10 items listed in each drug interaction monograph consisted of the drug interaction pair, severity, onset, effects, management options, monitoring guidance suggested by the investigators, patient’s reactions due to the drug pair, actual clinical management of adverse effects caused by the interaction, a description of the patient’s clinical course and responses following management, and a list of references documenting the specific interacting pair. In rare circumstances, if the data on severity category or any specific information regarding drug interactions were inconsistent in the different references, the most recent version of Drug Interaction Facts [13], available at the start of the study, was used as the primary reference.

During the study phase, all inpatient charts in the two psychiatric wards were checked for potential D-DIs on a daily basis over a 3-month period. The data collected from the charts consisted of demographic characteristics, disease state (diagnosed according to ICD-10 criteria [17]), current drug therapy and medication history, clinical symptoms and signs relevant to the study, laboratory test results, plasma drug concentrations (as appropriate), and length of hospital stay. Enrolled patients who stayed beyond the end of the study were monitored until discharged. The physicians in charge of the patients whose drug profiles suggested possible moderate or major drug interactions were provided with appropriate monographs during both the run-in and study periods.

The primary care teams were allowed to keep each monograph for an appropriate time period in order to assess the clinical progress of each patient and to file related observations on the monograph. These clinical responses evaluated by each primary care team constituted the primary assessment process for the study. Concomitantly, all the patients’ charts and nurses’ medication administration records were independently reviewed by a pharmacist-monitor, who also took part in the routine clinical discussions led by the attending physicians in order that the pharmacist-monitor could better understand the patient’s condition. The information collected by the pharmacist-monitor and the monographs gathered from the physicians were used in the secondary assessment by a three-member panel consisting of a psychopharmacologist, a pharmacologist, and a pharmacist. A flowchart of the study design is shown in the Figure.

**Assessments**

The assessment of actual or clinically significant drug interactions consisted of two steps, the primary and secondary assessments, as described above. D-DIs were considered to have occurred if suggestive clinical symptoms or altered drug effects were seen or confirmatory laboratory test results obtained. All suspected reactions filed by the primary care teams were verified by the three-member committee to determine if the reactions were a direct consequence of D-DIs on the basis of the data provided by the physicians and the pharmacist-monitor.

**Results**

During the 3-month study period, 155 patients were admitted to the two psychiatric wards of NTUH. However, three of these were only prescribed a single medication and were therefore excluded from the study, leaving 152 patients, 68
males and 84 females, in the study. A total of 537 medication profiles were collected and checked for interaction potentials during the study period.

Potential moderate or major severity D-DIs were identified in 79 (52.0%) of the 152 patients. A total of 130 potential interactions were detected in 339 drug profiles (63.1% of all medication profiles). Drugs that exhibited a greater propensity to interact with other medications included haloperidol (32 occurrences, 24.6%), trihexyphenidyl (32 occurrences, 24.6%), and trazodone (24 occurrences, 18.5%). The most frequently identified D-DI pair was haloperidol with anticholinergics (16.9%), followed by phenothiazines with anticholinergics (13.8%), and selective serotonin reuptake inhibitors with trazodone (13.8%).

The primary care teams reported 17 reactions in 15 patients who demonstrated undesired clinical responses similar to those described in the drug interaction monographs (Table). These responses included adverse reactions (hypotension, bradycardia, urinary retention, constipation, tremor, extrapyramidal symptoms, disorientation, and ataxia) and reduction or absence of therapeutic efficacy. A need for close patient monitoring (88.2%), management with antagonistic drugs (29.4%), altered dosage or discontinuation of at least one of the drugs (17.6%), use of alternative drugs (11.8%), or the temporal separation of administration of the interacting agents (5.9%) were documented by the primary care teams.

Of these 17 instances reported as clinically significant following primary assessment, only two, elicited in two different patients, were determined to be clearly due to D-DIs during the secondary assessment. The interacting drug pairs were trazodone with chlorpromazine [18] and doxepin with paroxetine. In each case, the patient developed orthostatic hypotension with drowsiness, dizziness, and an unsteady gait or a fall. The incidence of actual D-DIs was therefore 1.3% in all enrolled subjects (n = 152) and 2.1% in those with medication profiles showing D-DI potential (n = 79).

### Discussion

The aim of this study was to use a clearly defined mechanistic approach to prospectively investigate the incidences of both potential and actual D-DIs in a psychiatric inpatient population. The study employed drug interaction monographs and a two-stage assessment approach in determining actual D-DIs. The provision of primary care teams with interaction monographs containing information pertinent to the study ensured that the physicians were fully aware of their patients' potential for drug interactions. These specially constructed monographs, not used in other interaction studies with a similar aim, might have helped to minimize bias and increase detection sensitivity. In the primary assessment, 17 clinically significant D-DIs were reported, but, on secondary assessment, only two were recognized as being directly drug interaction-related, suggesting that a two-stage evaluation scheme is crucial for determining actual D-DIs objectively. Because actual interactions were observed in only two patients, there were insufficient data to allow risk factor analysis for specific interacting drug pairs and further clinical study is needed to determine these factors.

Hospitalized psychiatric patients commonly receive several therapeutic agents concurrently (often multicomponent medications). In certain situations, the use of a substantial portion of these drug combinations might be justified, such as...
the combination of anticholinergics with antipsychotics to attenuate extrapyramidal symptoms, antipsychotics with antidepressants for the treatment of psychotic depression, and mood stabilizers with antipsychotics or antidepressants for the treatment of bipolar disorder. Nevertheless, it is important for psychiatrists and their patients to be aware of drug interaction hazards, preventive measures, and management approaches.

The general applicability of the D-DI detection method used in this study to routine practice will depend on the availability of knowledgeable professionals involved in patient care as well as experts who specialize in drug interactions. On the other hand, healthcare institutions could also consider integrating certain approaches used in the study, including screening for interaction potentials following prescribing, providing healthcare providers with adequate information on drug interactions, and close monitoring of clinical progress by healthcare professionals, via their institutional health informatics systems. In this way, the achievement of the ultimate goals of undesired adverse drug interaction prevention, patient outcome improvement, and medical cost reduction would be achieved effectively.

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References