Distinguishing Drug Toxicity Syndromes From Medical Diseases: A QMR Computer-Based Approach

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ABSTRACT

Drug effects can mimic a wide variety of diseases. Experts note that adverse drug reactions (ADRs) have become the "greatest imitator" of disease in clinical medicine. Quick Medical Reference (QMR) is a decision support system providing diagnostic data about more than 600 medical diseases. Currently QMR contains only limited drug information. Just as physicians have difficulty diagnosing ADRs, QMR has similar problems in differentiating natural disease manifestations from drug toxicity syndromes. To remedy this problem, two prototype Drug Syndromes (DS), Carbamazepine Toxicity and Penicillin Toxicity, were incorporated into the QMR Knowledge Base (KB). Using detailed case reports, we demonstrated that a DS-augmented version of QMR was successful in discriminating these DS from the other diseases in QMR's KB. The addition of DS significantly improves QMR's diagnostic performance in cases in which some of the pathologic features are the consequence of drugs.

INTRODUCTION

Drug effects can mimic a wide variety of the diseases treated by internists. Karch and Lasagna, in a comprehensive review of the adverse drug reaction (ADR) literature, found that "there are major difficulties in discerning whether a particular event in a given patient is the result of a specific medication or part of the patient's underlying illness. The problem is further complicated by the fact that most patients who experience drug reactions often have been receiving many medications and frequently have several underlying illnesses that might account for the particular symptom or laboratory result attributed to the drug."[1] The chairman of the British Committee on Safety of Medicines recently remarked that, "Drug-induced diseases can mimic practically every naturally occurring disease. [Now] it would seem that the adverse drug reaction is the great simulator of diseases, a constant threat to the unwary physician."[2] In view of this fundamental problem which complicates all evaluations of drug therapy, it is not surprising that drug-induced illnesses pose many problems for computer-assisted medical diagnostic programs such as Quick Medical Reference (QMR).[3-4] Just as clinicians have difficulty diagnosing drug-related ailments, QMR --a diagnostic decision support system developed at the University of Pittsburgh-- has been empirically verified to have similar difficulty in separating natural disease manifestations from drug toxicity syndromes.

QMR is a microcomputer-based decision support program for diagnosis of challenging cases in Internal Medicine. The core of the QMR diagnostic program is a high-quality academic medical knowledge base (KB).[5-6] This large clinical KB currently provides diagnostic information about more than 600 diseases described by over 4,300 clinical Manifestations* (i.e., historical facts, patient symptoms, physical exam findings, and laboratory test results). In a recent clinical trial, QMR was found to be useful in analyzing difficult diagnostic problems posed by members of a general medicine ward team.[7]

BACKGROUND

Unfortunately, QMR can make critical diagnostic errors when it is applied to cases in which some of the pathologic features are the consequence of drug effects. Previous prospective work using QMR to analyze clinical pathologic conference (CPC) cases revealed a case in which quinidine-induced esophagitis with stricture[8] produced a top-ranked QMR diagnosis of Carcinoma of Esophagus. Unquestioned use of this QMR-generated diagnosis might lead to a risky, expensive, and time-consuming hospital course.

Subsequently, in a pilot experiment using classical clinical features of carbamazepine toxicity[9-11], QMR ranked the following diagnoses as the top four diagnostic competitors: 1) Brain Neoplasm Secondary Multiple, 2) Spongiform Encephalopathy, 3) Encephalitis Acute Viral, and 4) Cerebral Lymphoma Primary. This is a very grim

* QMR terms used here conform to the style used by the QMR program (e.g. first letter capitalized in "Manifestation," the "Hx" abbreviation for history, capitalization of the first word of a controlled vocabulary string describing a Manifestation, and capitalization of the first letter of each word in the title of a Disease Profile).

differential diagnosis for a disorder "cured" by decreasing the dose of a commonly prescribed anticonvulsant medication.

QMR's inability to differentiate natural from drug-induced disease is not surprising, if one considers the nature of the limited drug information currently contained in the QMR KB. This information is in the form of various historical Drug Administration Manifestations (e.g. ANTICOAGULANT Administration Prior to Current Illness Hx used in the QMR Disease Profile of Retroperitoneal Hemorrhage). There are 62 such drug Manifestations, and two types of Systemic Poisoning (Lead Poisoning and Arsenic Poisoning) utilized by the QMR diagnostic algorithm. Until the present time, there were no separate drug-induced syndromes in the KB. However, the program can diagnose certain drug-induced "naturally occurring" disorders [e.g. hydralazine as an etiology of systemic lupus erythematosus (SLE)]. Nevertheless, the current drug data in the QMR KB is perhaps best described as a by-product of previous QMR Disease Profiles not meant to process drug-related complications directly or comprehensively.

Such limited coverage of drug effects reduces QMR's usefulness in clinical situations. Many drug-induced diseases can be minimized by reducing or stopping an offending drug or by switching to alternative drugs. Thus, an important therapeutic opportunity is missed when drug-induced diseases are not included in a QMR differential diagnosis.

Assessment of previous classification schemes for ADRs for the purpose of adding integrated drug information to the QMR program and KB was performed. It was observed that each particular drug can cause a "family" of adverse effects. Savitsky recently summarized the traditional classification of ADRs: "Adverse drug reactions can be classified as Type A or Type B. Type A reactions produce 70% to 80% of ADRs, are dose dependent, and are related to the drug's pharmacology. Therefore these reactions should be predictable and probably preventable. Type B reactions, on the other hand, are idiosyncratic or allergic reactions, and are not dose dependent or related to the drug's pharmacology. For the most part, Type B reactions would not be predictable or avoidable."[12]

Drug toxicity syndromes are an important common group of Type A reactions. Two examples of Type A reactions to be used here are carbamazepine toxicity and penicillin toxicity. In contrast, anaphylactic shock is an important immunologically mediated example of a Type B drug reaction. This kind of drug reaction typically appears to be dose-independent because it is dose-dependent only with amounts far below the minimum therapeutic dose. In sensitized patients, tiny amounts of a drug can provoke life-threatening anaphylaxis. This usually precludes dose-response studies.

The exact assortment of drug-induced diseases associated with a given drug varies somewhat, but most drugs are capable of producing a toxicity syndrome in certain clinical situations. There are many factors which can increase the risk of drug poisoning. Some drugs have a "narrow therapeutic window" in which amounts not much greater than the recommended therapeutic doses can produce a drug toxicity syndrome. Advanced age, decreased rate of renal drug-excretion, diminished hepatic ability to metabolize drugs, concurrent or interacting drugs, multiple diseases, cognitive impairment, patient drug demand, physician prescribing behavior, and pharmaceutical company financial incentives are some factors which can increase the possibility of the occurrence of drug toxicity.[13] An increasingly common cause of drug toxicity is the deliberate acceptance of sometimes severe adverse drug effects as a "cost" of treating a fatal, dangerous, or severely debilitating illness.[14]

Another element contributing to the increasing risk of drug toxicity syndromes is the growing level of exposure to various medications. FDA surveys in 1985 regarding U.S. drug consumption found that, "The trend in overall drug use from 1971 to 1985 indicated that ... the population exposure to prescription drugs increased 29 per cent over this time period."[15] The large number of new drugs appearing on the market in recent years presents additional diagnostic challenges in the detection of novel drug toxicity syndromes (e.g. imipenem-cilastatin neuro-toxicity[16]). Knowledge of important drug toxicity syndromes is particularly pertinent for internists because of the volume of prescriptions they generate per patient encounter: 1.56 in 1981.[17]

METHODS

Considering the importance of drug toxicity syndromes (as well as allergic drug syndromes), we decided that the addition of ADR data to the QMR KB was a very desirable research focus. QMR-integrated drug information has the potential to significantly improve the diagnostic performance and clinical utility of the program. Stimulated by previous QMR diagnostic errors with quinidine-induced esophagitis and carbamazepine toxicity, we began adding Drug Syndrome (DS) information to the QMR KB.

CARBAMAZEPINE TOXICITY SYNDROME

In the first test, a DS Profile for Carbamazepine <TEGRETOL> Toxicity was designed. Recent clinical reviews[18-19], and standard sources[9-11] were used to construct this prototype DS. The initial hypothesis was that this additional drug information might permit QMR to differentiate Carbamazepine <TEGRETOL> Toxicity Syndrome from the more than 600 QMR diseases.

This prototype DS Profile uses the QMR Disease Profile format. Clinical diagnostic information is presented in the traditional case presentation style. Numbers preceding each Manifestation are the associated "evoking strength" (analogous to positive predictive value), and frequency value.[3] Figure 1 illustrates the new Carbamazepine Toxicity DS Profile.

Carbamazepine <TEGRETOL> Toxicity Syndrome

Past Medical History.. 6
0 2 AGE 16 To 25
0 3 AGE 26 To 55
0 1 AGE Gtr Than 55
2 5 CARBAMAZEPINE Administration Prior To Current Illness Hx
0 3 SEX Female
0 3 SEX Male
Symptoms of Current Illness................................ 3
1 4 EYE <S> Diplopia
1 2 VERTIGO
0 2 VOMITING Recent
Findings on Physical Examination.............................. 28
0 1 BEHAVIOR Agitated
0 1 BREATH Sound <S> Decreased Generalized
0 1 COMA
0 2 CONFUSION And/Or Disorientation
0 4 DELIRIUM
1 3 EXTREMITY <IES> Dysdiadochokinesis
0 2 EXTREMITY <IES> Exam Motor Or Muscle Abnormality
0 1 EXTREMITY <IES> Hemiballismus
0 1 EXTREMITY <IES> Movement Involuntary Distal Abrupt
0 1 EXTREMITY <IES> Movement Involuntary Proximal Writhing
2 5 EYE <S> Nystagmus
1 4 FINGER To Nose Test Abnormal
1 4 GAIT Ataxic
1 4 HEEL To Knee Test Abnormal
1 2 MOUTH Mucosa Dry <XEROSTOMIA>
0 1 MUSCLE <S> Facial Twitching
1 2 MUSCLE <S> Hypotonia Generalized
1 2 MUSCLE <S> Myoclonic Jerk <S>
0 2 NEUROLOGIC Exam Of Extremity <IES> Reflex <ES> Abnormal
0 1 POSTURE Opisthotonos
1 2 REFLEX <ES> Deep Tendon Decreased Generalized
1 2 REFLEX <ES> Deep Tendon Increased Generalized
0 1 SEIZURE Automatism <S> Face And/Or Extremity <IES>
1 2 SEIZURE <S> Grand Mal
0 2 STUPOR Lethargy Or Somnolence
0 2 TACHYCARDIA
1 4 TREMOR Action
0 1 TREMOR Resting
Simple, Inexpensive Laboratory Tests......................... 4
0 2 EKG Conduction Defect Present
0 1 GLYCOSURIA
0 1 KETONURIA
1 2 WBC Less Than 4000

Fig. 1 DS Profile for Carbamazepine Toxicity

Next, a recent case report of carbamazepine overdose (Patient 3)[19] was selected because it contained sufficient detail for QMR case analysis. QMR coding of case Manifestations is shown in Figure 2.

Positive Findings.. 9
Past Medical History..................................... 3
AGE 26 To 55
CARBAMAZEPINE Administration Prior To Current Illness Hx
SEX Female
Findings on Physical Examination.......................... 6
COMA
EXTREMITY <IES> Movement Involuntary Proximal Writhing
EYE <S> Nystagmus
GAIT Ataxic
REFLEX <ES> Deep Tendon Increased Generalized
STUPOR Lethargy Or Somnolence
Negative Findings 2
LEG <S> Sensation Pain Decreased
REFLEX Babinski Sign Present Bilateral

Fig. 2 QMR coding of a case report of Carbamazepine Toxicity

QMR was then utilized in Case Analysis mode to construct a differential diagnosis for this case using the drug information- augmented KB. The scoring of the top seven QMR diagnoses are listed in Figure 3.

Potentially Interesting Diagnostic Hypotheses..............37
197 Carbamazepine <TEGRETOL> Toxicity Syndrome
166 Cerebral Malaria
166 Encephalitis Acute Viral
166 Rickettsial Meningoencephalitis
166 Spongiform Encephalopathy Subacute
159 Wilsons Disease Of Central Nervous System
147 Multiple Sclerosis

Fig. 3 Top seven QMR diagnoses for a case report of Carbamazepine toxicity

Using this clinical case-specific data, QMR was now successful in selecting Carbamazepine <Tegretol> Toxicity Syndrome over the other diseases in the QMR KB.

PENICILLIN TOXICITY SYNDROME

A more difficult test was then devised to determine if a DS-modified version of the QMR KB could be used to distinguish concurrent natural disease from another drug toxicity syndrome. Penicillin Toxicity Syndrome was chosen to demonstrate the ubiquity of drug toxicity syndromes even with frequently used and highly non-toxic drugs. In his review of side effects of various antibiotics, Hoigne states, "The penicillin preparations are among the few antibiotics with bacteriocidal effect that, as a rule, are hardly toxic in man even when given in high doses."[20] Most other antibiotics are associated with more serious and more frequent toxic effects.

In 1981, 43% of all patients hospitalized in the United States received antibiotics. Of these, the penicillins were the largest group, comprising a total of 33.7 defined

daily doses per 100 hospital beds.[21] Lowe has calculated that "Today [1982] there is sufficient penicillin fermentation and production capacity worldwide to provide every individual on this planet with sufficient penicillin for one therapeutic treatment each year."[22] Thus, the magnitude of penicillin exposure in the U.S. is tremendous.

Neu gives a recent review of the spectrum of other penicillin-induced diseases, and characterization of the dozens of compounds in this group of antibiotics.[23] The focus here will be on penicillin toxicity. Mumenthaler has succinctly described this disorder: "Penicillin encephalopathy is a neurotoxic syndrome produced by high dose penicillin treatment (20 million units/day or more): myoclonic spasms, epileptic attacks and ever increasing disturbances of consciousness commence 24-48 hours after the start of treatment, and lead eventually to coma. These signs appear if the cerebral spinal fluid concentration of penicillin exceeds 10 U/ml."[24]

Other documented features of penicillin neurotoxicity include somnolence, hallucinations, hyperreflexia, and a variety of generalized electroencephalographic abnormalities, particularly diffuse slow wave activity. Typically the encephalopathy resolves quickly during the first few days after discontinuation of the drug. Previous clinical descriptions have not recorded premonitory symptoms or focal neurologic signs. There is no associated CSF pleocytosis or elevation of the CSF pressure. There are no characteristic autopsy findings associated with fatal penicillin toxicity.[25-28]

Penicillin applied to the brain surface or injected locally can produce seizure activity, and has been used in several experimental systems as models of epilepsy.[29] Intra-thecal instillation[30], large parenteral doses[31], renal impairment[32], cardiopulmonary bypass surgery[33], septicemia[34-35], and meningitis[36] are associated with an increased risk for penicillin neuro-toxicity. The key factors in these clinical situations are high blood concentrations of penicillin, and increased permeability of the blood-brain barrier.[37] Nephro-toxic drugs administered with penicillin, such as probenecid, phenylbutazone, and aminoglycosides, are known drug-induced causes of renal impairment which predispose patients to penicillin poisoning.[38]

Penicillin toxicity is limited almost entirely to hospital inpatients receiving parenteral penicillin. It has not been reported in outpatients or with oral administration. Jick and co-workers in a series of 12,617 medical inpatients enrolled in the Boston Collaborative Drug Surveillance Program (BCDSP) found that drug-induced convulsions occurred in 17 patients (overall risk of 1.3 per 1,000). Infusions of penicillin represented the third most common cause of drug-induced seizures. Grand-mal seizures occurred in 4 of 1245 patients receiving intravenous penicillin (3.2 per 1,000). None of these patients had a previous history of epilepsy. Only lidocaine and insulin were more frequent causes of drug-induced convulsions.[39]

These clinical features were compiled, producing the QMR DS depicted in Figure 4.

Penicillin Toxicity Syndrome

Past Medical History.................................... 9
0 2 AGE 16 To 25
0 3 AGE 26 To 55
0 3 AGE Gtr Than 55
0 1 BRAIN Surgery Recent Hx
0 1 HEART Surgery Recent Hx
1 5 PENICILLIN Product Administration Prior To Current Illness Hx
1 2 PROBENECID Administration Prior To Current Illness Hx
0 3 SEX Female
0 3 SEX Male
Symptoms of Current Illness................................ 2
1 2 HALLUCINATIONS Visual
0 3 ONSET Abrupt
Findings on Physical Examination............................. 10
0 1 COMA
0 4 CONFUSION And/Or Disorientation
0 4 DELIRIUM
0 4 EXTREMITY <IES> Exam Motor Or Muscle Abnormality
1 3 MUSCLE <S> Myoclonic Jerk <S>
0 4 NEUROLOGIC Exam Cerebral Dysfunction Present
0 3 NEUROLOGIC Exam Of Extremity <IES> Reflex <ES> Abnormal
1 3 REFLEX <ES> Deep Tendon Increased Generalized
1 3 SEIZURE <S> Grand Mal
0 2 STUPOR Lethargy Or Somnolence
Simple, Inexpensive Laboratory Tests...................... 2
1 3 CREATININE Serum Increased Not Over 2:9 Mg Per Dl
1 3 UREA Nitrogen Serum 30 To 59
Moderately Expensive and/or Invasive Laboratory Tests........ 2
1 3 EEG High Amplitude Slow Wave <S> Bilateral
1 3 EEG Low Amplitude Slow Wave <S> Bilateral

Fig. 4 DS Profile for Penicillin Toxicity

A suitable case of penicillin toxicity occurring during treatment for bacterial endocarditis was discovered in the Neurology literature.[40] This case further illustrates the possibility for diagnostic error caused by omission of drug information from the QMR KB, and demonstrates improved QMR diagnostic performance after addition of DS to the QMR KB.

A synopsis of this case follows:

The patient was a 71 year-old white female with a 5 week history of fever, chills, lethargy, weight loss, splenomegaly, petechiae, and a grade II/VI apical blowing systolic murmur radiating to the axilla. Laboratory tests were largely normal except for a polymorphonuclear leucocytosis, and slight hematuria and pyuria. Despite negative blood cultures, she was treated with probenecid and increasingly large doses of penicillin for a presumptive diagnosis of bacterial endocarditis.

All significant clinical data specified in this case report could be converted into the original QMR terminology, with the exception of information related to penicillin therapy. The importance of the large doses of penicillin used, the penicillin levels in body fluids, and the effect of probenecid in elevating penicillin levels (by decreasing renal excretion) could not be represented by QMR.

This case-specific information was translated into QMR's controlled vocabulary for the purpose of case analysis. Figure 5 shows the 23 Positive Findings.

Past Medical History.. 6
AGE Gtr Than 55
HYSTERECTOMY Hx
RACE White <CAUCASIAN>
SEX Female
URINARY Calculus Hx
WEIGHT Loss Gtr Than 10 Percent
Symptoms of Current Illness................................ 1
HEADACHE Severe
Findings on Physical Examination........................... 7
FEVER
HEART Murmur Holosystolic Apical
RIGOR <S>
SKIN Petechiae
SPLENOMEGALY Slight
STUPOR Lethargy Or Somnolence
TACHYCARDIA
Simple, Inexpensive Laboratory Tests........................ 9
CHEST Xray Pleural Thickening Laminar
EKG Sinus Tachycardia
EKG Ventricular Premature Contraction <S>
HEART Xray Left Ventricle Enlarged
HEMOGLOBIN Blood Less Than 12
UREA Nitrogen Serum 30 To 59
URINE Sediment Rbc
URINE Sediment Wbc
WBC 14000 To 30000
(There were also 74 Negative Findings coded.)

Fig. 5 QMR coding of a case report of suspected endocarditis

Prior to modification of the QMR KB with DS, the leading QMR diagnosis was in agreement with the patient's physicians, left heart endocarditis. On the twenty-third hospital day, penicillin doses were increased from 20 to 30 million units/day because of persistent fever to 102 degrees. On the twenty-ninth hospital day, the patient became mildly confused. By the thirty-second hospital day, she had become more confused with lethargy, stupor, and occasional hallucinations. She had also developed continuous gross muscle jerks (myoclonus), and muscle twitching. A lumbar puncture revealed normal findings. An EEG showed marked diffuse slow activity. At that time, a neurology consultant suspected penicillin toxicity, and penicillin was stopped.

This turn of events was translated into QMR terms still using the original QMR KB. Using all prior case manifestation plus the new findings of penicillin toxicity, QMR now ranked Goodpasture Syndrome <Renal Component> as the leading diagnosis with Endocarditis Acute Infective Left Heart, and Endocarditis Subacute Infective Left Heart trailing by just a few points. Endocarditis Subacute Infective Left Heart consistent with the patient's clinical course was Asserted, and pertinent "explained" Manifestations were deleted from the case. Now the top-ranked QMR diagnoses were Spongiform Encephalopathy and Epilepsy Idiopathic Grand Mal. These results demonstrate that a life-threatening episode of penicillin toxicity is erroneously attributed to various QMR diseases by a version of QMR lacking information about drug toxicity syndromes.

In fact, the patient steadily improved after penicillin was stopped. She was discharged to home seven days later. Her electroencephalogram had reverted to normal activity. She was afebrile with a normal general neurologic examination, but formal memory testing revealed retrograde amnesia during the period of maximal penicillin neurotoxicity.

It was next postulated that the addition of both Penicillin Toxicity Syndrome and Carbamazepine Toxicity Syndrome would improve the diagnostic accuracy of QMR in regard to this case. More specifically, It was predicted that a DS-modified version of QMR could distinguish Penicillin Toxicity from Carbamazepine Toxicity, and differentiate it from the other diseases represented in the KB. It was also hoped that the underlying features of endocarditis would not be diagnostically obscured.

Next using the same case Manifestations presented earlier, and the KB augmented with the two new DSs, QMR was again used in the case analysis mode. Again Endocarditis Subacute Infective Left Heart consistent with the patient's clinical course was Asserted, and the case analysis algorithm was recycled on the remaining unexplained Manifestations. A listing of the resulting top twelve QMR-generated diagnoses is shown in Figure 6.

Previously Asserted Diagnoses................................ 1
Endocarditis Subacute Infective Left Heart

Potentially Interesting Diagnostic Hypotheses............... 31
121 Penicillin Toxicity Syndrome
116 Glomerulonephritis Focal
100 Glomerulonephritis Acute
96 Spongiform Encephalopathy Subacute
88 Migraine
87 Epilepsy Idiopathic Grand Mal
86 Epilepsy Idiopathic Psychomotor
78 Goodpasture Syndrome <RENAL COMPONENT>
73 Alzheimers Disease
72 Arteriolar Nephrosclerosis Malignant <MALIGNANT HYPERTENSION>
71 Schizophrenia
70 Aortic Regurgitation Chronic
69 Mitral Regurgitation Rheumatic

Fig. 6 QMR diagnoses for a case report of Endocarditis with Penicillin Toxicity: DS version

After addition of the DSs, QMR was successful in ranking Penicillin Toxicity as the leading diagnosis in this case.

CONCLUSION AND FUTURE DIRECTIONS

Thus, it was experimentally demonstrated that QMR computer-assisted diagnostic analysis of complex clinical cases can be significantly improved by adding information about drug toxicity syndromes.

Encouraged by this improved diagnostic performance with the DS version of QMR, work was begun on a QMR-integrated clinical pharmacology module. This drug KB, called QMRx, will be composed of DS Profiles similar in format to that of Penicillin Toxicity Syndrome and Carbamazepine <TEGRETOL> Toxicity Syndrome presented here. It will use a super-set of the QMR controlled vocabulary. For each drug, a group of DSs classified by mechanisms will form a QMRx DS "Family." This modular design is intended to promote steady incremental growth of the QMRx clinical pharmacology KB.

Three major strategies are being used for this development process:

1). Selective use of existing electronic drug information (as well as traditional paper sources) to assist in the creation of the QMRx KB by providing:
   A) bibliographic guides for reviews of the clinical drug literature,
   B) current therapeutic indications for a drug,
   C) current drug dosage recommendations, and
   D) ready access to electronic medical textbooks.[41]

2). QMRx DS will be composed of easily segmented and relatively small (compared to Disease Profiles) collections of clinical information. A common classification scheme based on pharmacologic and immunologic mechanisms will be used.[42-43] Due to their smaller size and repetitive organization, comprehensive DS reviews of the clinical pharmacology literature can be completed in less time. Additional DSs regarding a particular drug can be added later to form a DS "Family."

3). The Quick Medical Reference Knowledge acquisition Tool (QMR-KAT)[44] is being used to develop a QMR Disease Profile for anaphylaxis. The two leading causes of this syndrome are medications (especially penicillin) and insect stings.[45] This Disease Profile will then be modified to address only drug-induced causes of anaphylaxis for the QMRx KB. QMR-KAT allows ready access to the QMR KB while creating Disease Profiles or DS Profiles, bibliographic linking, and a measure of standardization for new controlled vocabulary phrases.

4). When deciding which DS s to profile next, a number of factors will be considered:
   A) the number of prescriptions written,
   B) the frequency of the DS,
   C) the severity of the DS,
   D) whether the drug has a small therapeutic window, and
   E) whether this DS can be confused with a QMR disease.

As this planning proceeds, the magnitude of the QMRx knowledge engineering task is growing rapidly as traditional chemically synthesized drugs and new biotechnology drugs proliferate. According to Manasse there were 656 drugs available in 1961, but there are approximately 8,000 drugs in use today. From 1975 to 1987, the FDA approved 270 "new molecular entities" (NME) for an average of 21 NME per year. As of mid-1989, there was a backlog of 73 applications for NME licensing. In addition there were 14 new genetically engineered drugs awaiting FDA approval, and at least 67 more in human clinical trials.[46] Consequently, ADRs are expected to increase, and future U.S. physicians will require more training in clinical pharmacology to cope with a deluge of information about new drugs.[47]

ADR analysis programs[48-49] as well as computer-assisted medical diagnostic programs such as QMR have the potential to be important tools for managing the drug information glut. QMRx is designed to help differentiate drug effects from disease effects. This is a process central to accurate diagnosis of both medical diseases and ADRs.[50] The creation of the Carbamazepine <Tegretol> Toxicity and Penicillin Toxicity DS are promising first steps in QMR computer-assisted diagnosis of drug-induced diseases.

ACKNOWLEDGEMENTS: This research has been supported by a National Library of Medicine Fellowship and NLM Grant T15LM07059. Nunzia Giuse, M.D., Dario Giuse, Ph.D. and Jerome Osheroff, M.D. provided suggestions and editorial comments on the final draft.

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