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27

SUDDEN DEATH IN PSYCHIATRIC PATIENTS: THE ROLE OF NEUROLEPTIC DRUGS

An American Psychiatric Association Task Force Report

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George H. Pollock, M.D.
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TABLE OF CONTENTS

INTRODUCTION

Sudden, unexpected death may occur in apparently healthy individuals. Its occurrence in psychiatric patients has raised the concern that the use of psychotropics, especially antipsychotics, may be associated with an increased risk for sudden death. This concern is maintained even though not all psychiatric patients who have succumbed to sudden death have been on psychotropics.

Early reports presented the concern that the use of chlorpromazine and thioridazine were associated with sudden death. More recently, the focus shifted to the more potent agents. Indeed, the FDA Advisory Committee discussed the possibility of a connection between sudden death and haloperidol. No decision could be reached by the FDA Committee because of the enormous complexity of the problem. Nonetheless, since sudden death continues catastrophically to complicate the course of some patients, the Task Force on Sudden Death was formed to investigate further the relationship of antipsychotic agents and sudden death.

This is a difficult issue to explore for many reasons. It demands a knowledge of incidence of sudden death in the normal population compared to the psychiatric population both before and after psychotropics were introduced. Obtaining these data is complicated by the fact that the term "sudden death" has been given widely varying definitions. Thus, the use of standardized definitions and comparison of age, sex and otherwise matched population is necessary to determine if, in fact, a relationship between antipsychotic administration and sudden death exists.

In addition, the issue of stress and sudden death needs to be examined. Stress itself is difficult to define, but folklore and, indeed, data suggest that sudden bad or good news can produce sudden death. Similarly, excessive physical exercise, e.g., the annual opening of football camps, results in sudden death in apparently healthy athletes, Adding the consideration of stress to the examination of the relationship between antipsychotics and sudden death in psychiatric patients makes matters even more complex. If there is an association between neuroleptics and sudden death, these patients would comprise a high risk population. On the other hand, they may also be at high risk for stress-induced sudden death in which case antipsychotics may be protective. To complicate things further, the stress that psychotic patients endure is quite difficult to assess and quantify. The charge to the Task Force was to evaluate the relative weight and interactions of these factors against the background of an acceptable definition of sudden death. This involved consideration of the various causes of sudden death together with potential drug-induced mechanisms and risk factors. Finally, the Task Force considered recommendations that might favorably affect the risk/benefit ratio and the possible ways of obtaining more information on the subject.

DEFINITIONS

The subject of sudden death has been of concern to and studied by the medical profession for many years. The term "sudden death" sounds rather unambiguous -- an apparently healthy person rather abruptly collapses and rapidly expires. For epidemiological purposes, however, a more precise definition is necessary. Unfortunately, there is no widely accepted, standardized definition that would permit reliable cross-study comparisons of the type essential to evaluating a specific area such as psychotropic drug-related sudden death.

The prototypic psychotropic drug-related sudden death might be a hospitalized psychiatric patient with no known medical illness who, early in the course of parenteral treatment with an antipsychotic drug and while under close observation, is found dead minutes after being last seen and in whom, after a meticulous post-mortem examination, no cause of death can be established; hence, an unexplained, unexpected, sudden, natural death. If psychotropic drugs could be unequivocally implicated in causing such deaths, the term "unexplained" would no longer be appropriate. Often in the absence of an alternative explanation, the relationship between the medication and the death is assumed to be causal rather than coincidental. An analogy can be made with the patient with puzzling symptoms in whom a physical evaluation is unrevealing and who is, therefore, assumed to have a psychological illness. Such an assumption mayor may not be correct, for a nonpsychiatric medical illness may still be causal yet remain undetected for lack of appropriate diagnostic procedures (Jefferson and Marshall, 1981).

Death

In recent years, a considerable amount of medical and legal effort has gone into establishing a precise definition of death. While controversy remains with regard to the finer points, an uncomplicated definition could suffice for the purposes of this report (i.e., death -- the permanent cessation of all vital body functions).

Natural Death

The distinction between traumatic (unnatural) and natural death seems clear from a definitional point of view although establishing into which category to place a death may be troublesome. Natural deaths have been defined as having non-violent or non-traumatic causes (Kuller, 1966; Kuller, et al., 1966; 1967), or in a somewhat circular fashion as the deaths remaining after exclusion of those "who an autopsy would determine to have died from other than natural disease" (Luke and Halpern, 1968). Burch and DePasquale (1965) excluded deaths due to "physical trauma, poisoning, drug reactions or therapeutic procedures" to establish their definition of natural death.

Sudden Death

As succinctly stated by Pisa (1980), "The reviews of the extensive literature on sudden death agree unanimously that there is a great inconsistency in definitions of sudden death, and that therefore comparisons and uniform interpretation of results from different studies are, at the present time, extremely difficult." In other words, "how sudden is sudden?"

Most studies define "sudden" as occurring 24 hours or less from the onset of symptoms. There is disagreement as to whether death that occurs rapidly following an exacerbation or complication of a pre-existing illness should be considered sudden death (Kuller, et al., 1967). There is also disagreement as to the time interval between symptoms and death. For example, the following definitions have been used:

1. "An instantaneous death that is occurring within a few minutes of the onset of clinical manifestations" (in Pisa, 1980) .

2. "Death occurring instantaneously or within an estimated 24 hours of the onset of acute symptoms or signs" (in Pisa, 1980).

3. "Non-violent death occurring unexpectedly within six hours in an apparently healthy subject, or in a sick person whose condition was either steady or improving" (in Pisa, 1980).

4. "An individual who died due to natural causes and who was not restricted to his home, a hospital, or an institution, or unable to function in the community for more than 24 hours prior to death and which 1he time interval from the onset of the fatal event was less than 24 hours." [Based on this definition, one can appreciate that this study, "An Epidemiological Study of Sudden and Unexpected Death in Adults," (Kuller, et al., 1967) would involve a population quite different from the population in which most psychotropic drug associated sudden deaths have been described.]

Kuller (1966) points out that it is often difficult to establish time of onset of symptoms, especially if death occurs unobserved. He also reviews a number of studies in which the term "sudden" was defined by intervals from onset of symptoms to death of less than one hour, one hour, two hours, twelve hours, and twenty-four hours.

One of the better studies of neuroleptic drug-related sudden death used as a definition "an apparently healthy person's death occurring literally instantaneously or within one hour of the onset of the symptoms, excluding suicide, homicide, and accident" (Ungvairi, 1980).

The definition of the term "sudden death" has also been handled by avoiding a definition and, instead, suggesting that each case be dealt with by recording time elapsed between onset of symptoms and death {Pisa, 1980} .

In.summary, definitional issues abound. Myerberg concludes: "Thus, it is not possible to give a single best definition for the syndrome. However, a broad definition of sudden death might be stated as natural death, occurring instantaneously, or within one hour of the onset of symptoms, in a patient who may or may not have known pre-existing disease but in whom the time and mode of death come unexpectedly. The three terms that should stand out in any definition of sudden death are (1) natural, (2) unexpected, and (3) rapid. For epidemiologic purposes, there is some value to extending the time limit for actual biologic death to 24 hours after the onset of a pathophysiologic process such as ventricular fibrillation, the occurrence of which may have led to irreversible damage inexorably leading to death" (Myerberg, 1978).

Retrospectively applying a reasonable but nonetheless arbitrary set of criteria to a markedly heterogenous literature data base is, in itself, a difficult task requiring judgment decisions when information is unclear or lacking. A different, but equally valid, set of criteria applied to the same base would be expected to produce a study population that, while similar, would not be the same. Finally, a review of this type excludes other sudden death patient pools including (1) cases reported, sometimes in great detail, to pharmaceutical houses and the FDA but which do not reach the scientific literature and (2) what must be assumed to represent an even greater unseen part of the problem-those cases not reported at all.

Expected vs. Unexpected Death

A natural death, even were it to meet any or all of the many definitions of "sudden," would be excluded from many studies if it were categorized as "expected." A precise distinction between expected and unexpected sudden death does not exist and definitional boundaries are blurred. Expected can be defined as "considered probable or certain" and unexpected as "unforeseen" (Webster's Ninth New Collegiate Dictionary, 1983).

Burch and DePasquale (1965) feel that the unexpected nature of the event is the essential element in sudden death and while the person need not be in excellent health prior to the event, the event occurs at a time at which there appears to be no immediate danger of death. One is left with the task of defining "immediate" in order to distinguish the unexpected from the expected and the same definitional blurring remains.

Kuller, et al. (1967) also use the unexpected nature of the event as a necessary definitional aspect of sudden death. They state "the degree of disability prior to death was used as a measure of the expectation of death." In their study, they defined as unexpected those deaths occurring

in individuals who were not confined to their home, hospital, or other institution because of illness more than 24 hours prior to death.

Often the term "unexpected" is not defined (Myerberg, 1978; Luke and Halpem 1968; Lundberg and Voigt, 1979; Pisa, 1980) in spite of it being an important qualifier in defining the population under study. Certainly, "expectedness" of a death is partially in the eyes of the beholder and defined to a great extent by the information the evaluator has at his disposal. For example, a bystander might view a death as unexpected when witnessing an apparently healthy middle-aged man drop dead in the street while the decedent's physician, armed with a history of severe unremitting coronary artery disease, might consider the event quite predictable and expected.

Explained vs. Unexplained Death

There is some overlap between these terms and those discussed above. What can be explained is often anticipated and what is unexplained is often unexpected. An effort to establish the cause of death is a necessary aspect of the evaluation of sudden, unexpected deaths. For example, the role of a neuroleptic drug in the death of an apparently healthy twenty year old would be viewed quite differently (1) if no autopsy was performed, (2) if an autopsy was unrevealing, or (3) if a ruptured thoracic aortic aneurysm was discovered at autopsy.

Troublesome unknowns in the evaluation of sudden death are the total frequency of sudden death in a population, the percent of those cases that are referred to the medical examiner for autopsy, and the selection process that determines which cases are autopsied and which are not. This must vary considerably from community to community and consequently, suggests that data generated from a particular series of autopsy cases may not be applicable to a different population or generalized to a population as a whole. Kuller (1966) states: "The total number of sudden deaths that occur in a defined population and their distribution in relation to a variety of demographic variables are unknown. The data from the Medical Examiner's Office may be a biased sample of all sudden deaths since it is quite possible that cases of sudden death and unexpected death in the upper socioeconomic groups may be less likely to be referred to the Medical Examiner. Furthermore, it is probable that not all Medical Examiner cases are sudden deaths but that some are really medically unattended deaths."

The value and reliability of the autopsy in establishing cause of death has been questioned, especially with regard to drug-related deaths. Concern has been expressed in two areas: (1) the thoroughness of the examination and (2) a lack of distinction between association and cause. With regard to the former, James, et al. (1976) examined in detail the hearts of two young athletes (ages 15 and 18 years) who had died suddenly and unexpectedly and in whom routine autopsy had provided no explanation. In both cases, histopathology of the cardiac conduction system was found that suggested a lethal arrhythmia as the cause of death. In a sense, the unexplained became explained although the most thorough autopsy cannot answer the question of' "why now?" Had those two young persons been receiving antipsychotic drugs at the time of death, the drugs might have been viewed as causal (especially after routine autopsy was unrevealing), coincidental (sudden, unexpected death does occur in this age group in the absence of medication), or provocative (the specialized autopsy finding of pre-existing disease with the drug acting as a trigger to explain the "why now?").

Leber (1981) challenges "the time honored tradition among many pathologists" always to provide a cause of death. For example, Lundberg and Voigt (1979) found a cause for death in all of 100 consecutive adults who had died suddenly and unexpectedly. In a series of unexpected natural deaths in young adults, a cause of death was found in all 275 consecutively autopsied cases (Luke and Halpern, 1968). There must be a distinction between the presence of a disease and death caused by a particular disease and while one might not quarrel with the finding of a massive upper GI hemorrhage as the cause of death, the association of coronary artery disease and death may be less clear. Killip (1975) states:

"Although the vast majority of adults who die suddenly have evidence of coronary artery disease, it would be inaccurate to assume that this finding provides a ready explanation for the event ... In some instances, the coronary artery abnormalities may be irrelevant to the final event."

Leber (1981) suggests that the need to provide a cause of death may unjustly assign cause of death to a drug only because of insufficient anatomical evidence to provide an alternative diagnosis. He states "in short, it is the autopsy which yields the least anatomical evidence to explain a death that is most likely to be used to argue the case that a neuroleptic caused the death."

In their study of precursors of sudden coronary death, Kannel, et al. (1975) assumed by definition that all sudden deaths were due to coronary heart disease when "an apparently well person was observed to collapse and expire within one hour of onset of symptoms, usually in a matter of minutes, where no other cause was suggested by the medical history." As the length of time increases between onset of symptoms and death, causes other than coronary heart disease become more likely (Kuller, et al. 1967). These include cerebrovascular disease, rheumatic heart disease, pulmonary embolism, and alcoholism and fatty liver.

Sudden death is a difficult subject to define, let alone study. Factors that have impaired a better understanding of sudden death in general and drug-related sudden death in particular are: lack of standardized definitions, heterogenous populations from which data bases are generated, inconsistencies in both obtaining and conducting a thorough autopsy, the inability to obtain information from the deceased, the absence of reliable witnesses, and incomplete data collection.

INCIDENCE OF SUDDEN DEATH

Overall, between 15-30% of all natural deaths occur suddenly and unexpectedly (Kannel, et al., 1975). Obtaining a more precise figure has not been possible because of biases and variables inherent in studies of this type.

Estimates of the total number of sudden, unexpected natural deaths in the United States alone range from 300,000 to 500,000/year (Doyle, 1976; Horowitz and Morganroth, 1982; Kannel and Thomas, 1982) and studies tend to focus on coronary artery disease as the major cause of these deaths (Kuller, 1966; Kuller, et al., 1966; Kuller, et al., 1967). Despite inconsistencies in data collection and reporting, autopsy studies consistently report between 45% and 66% of sudden, unexpected deaths to be due to diseases of the heart and aorta (Kuller, 1966; Kuller, et al., 1966; Kuller, et al., 1967). The abruptness of sudden death also influences the percentages attributed to cardiovascular causes with estimates that 80-90% of deaths occurring within 24 hours of symptom onset are caused by cardiovascular disease (Burch and DePasquale, 1965).

A CRITICAL REVIEW OF CASE REPORTS OF SUDDEN DEATH

Do psychiatric patients receiving psychotropic drugs have a higher mortality than the general population? Evidence for this is inconsistent. Richardson (1966) estimated that there might be one or two cases of unexpected sudden death in a 2,000 bed psychiatric hospital over an 11 year period. In fact, this figure is not significantly higher than that of a normal population. Swett and Shader (1977) in a prospective study monitored a random sample of 1832 consecutively admitted psychiatric patients in order to estimate both the rate of cardiac side effects and sudden death associated with psychotropic medications. There were two sudden deaths in this group, neither of which were attributed to tricyclic antidepressants or phenothiazines. The small sample size of each of the above studies limits any firm conclusions and is at odds with the report of Craig and Lin (1981) [reported in detail on p. 11] which found no difference in mortality rates between the pre- and post-neuroleptic period, but nonetheless found a higher mortality rate in both periods than that in the general population.

Sudden, unexpected and unexplained deaths during psychotropic drug therapy, particularly phenothiazine therapy, have often been reported (Zlotlow, 1958; Reinert, 1960; Kelley, 1963; Roizin, 1963; Hollister, 1965; Moore, 1969; Ungvari, 1980). Examining the literature, we find many of these cases did not meet the definition of sudden, unexpected and unexplained death (10). Some did not die suddenly. Some had pre-existing life-threatening diseases. Thus, their deaths could not be described as unexpected. Furthermore, a great proportion of these decedents had positive autopsy findings to which the fatal outcome might be attributed, such as coronary artery disease, asphyxia, aspiration, pulmonary embolus, intestinal obstruction or paralytic ileus. It is incorrect to designate such deaths as unexplained.

In order to assess objectively the relationship of psychotropic drugs and sudden death, Zhang and Davis (unpublished data) established criteria for unexpected, unexplained sudden death, q.v. These were "(1) the death is sudden when it was discovered less than 24 hours after the decedent was last seen alive; (2) the patient was physically healthy, had no pre-existing life-threatening illnesses, particularly no cardiac diseases; (3) the patient received usual dosages of psychotropic drugs; (4) the result of the autopsy was negative, there were no findings which could explain the cause of death; (5) the data of the patient were relatively complete and available for analysis." Using these criteria, they found only 35 cases of psychotropic drug-related unexpected, otherwise unexplained sudden death in the English literature between 1957 and 1980; 21 were males, 14 females, ages 20-70 years. Of them 80% were between 25-54 and the average age was 39.9. Sixteen (45.7%) were taking chlorpromazine alone at the time of death; four cases (11.4%) thioridazine; three cases (8.6%) trifluoperazine; two cases (5.7%) prochlorperazine; and one case (2.9%) perphenazine, fluphenazine, haloperidol, carphenazine or levomepromazine, respectively. Five cases (14.5%) were taking two or more psychotropic drugs; two cases chlorpromazine and thioridazine; one case trifluoperazine and fluphenazine; one case chlorpromazine and trifluphenazine and haloperidol; and one case thioridazine combined with imipramine and desipramine. The frequency of drugs used was concordant with the frequency of those used in psychiatric patients at that time. Chlorpromazine is the leading drug, particularly in the earlier papers, and high potency agents were reported more frequently in recent articles. Because cases of overdosage with psychotropic drugs were excluded, the dosage of psychotropic drugs were moderate and usually within the accepted therapeutic range. Twenty (57.1%) were described as found dead; eight (22.8%) had some evidence of collapse; seven (20.0%) had seizures and three (8.6%) had difficulty in breathing just before their death.

The autopsy findings were generally nonspecific (e.g., dilation of heart, congestion and edema of lungs, congestion of viscera) and not helpful in establishing an anatomic cause of death. The only exception was Richardson (1966) who found collections of mucopolysaccharide materials in the smaller arterioles of the heart's subendocardial region. The clinical significance of such findings is unknown and these observations have never been confirmed.

Cardiac arrhythmia, cardiac arrest and sudden catastrophic hypotension related to antipsychotic drugs have been suggested as possible mechanisms. Both cardiac and hypotensive effects of antipsychotic drugs will be discussed later.

The 31,960 admissions to the Shanghai Psychiatric Hospital (Zhang and Zhou, unpublished, personal communication) from 1970-1979 were examined, and of these, 39 patients died suddenly while receiving treatment with psychotropic drugs. Eighteen of these were explained by pathological findings such as heart disease, asphyxia, infections, megacolon, and other causes. Only 21 cases were classified as unexplained sudden death. Neither the total mortality nor the unexplained sudden deaths was higher than that of the general population.

A report of data gathered by the Registry of Tissue Reactions to Drugs examined lethal adverse drug reactions (Irey, 1976). There were 220 validated cases of unexpected and unpredictable deaths with half occurring between the ages of 21-50. Psychotropic drugs (not further defined) were the third most commonly implicated drug category (18 cases) but lagged far behind anti-infective agents (76 cases) and anesthetics (42 cases). With regard to the ten most frequently involved specific drugs, chlorpromazine was the only psychiatric drug and ranked fourth (9 cases) behind halothane (28 cases), penicillin (28 cases) and tetracycline (12 cases). Aspirin did not lag far behind (5 cases). This report did not address the issue of sudden versus non-sudden death and provided no information as to the frequency of use of individual drugs or drug classes so no conclusions can be drawn with regard to the true incidence of drug-related sudden death. The report does serve as a reminder that the use of all classes of drugs carries a small but real risk of serious untoward reactions and that the risks associated with psychotropic drugs must be viewed against this background.

Sudden, unexpected, natural death occurs in all age groups. The sudden infant death syndrome is a grim reminder that even the very young are not spared. It was recently reported that syrups containing phenothiazines were prescribed significantly more often in sudden infant death syndrome victims suffering from nasopharyngitis than in controls similarly afflicted but not prescribed phenothiazines, leading to the postulation that these drugs may contribute to the occurrence of the syndrome (Kahn and Blum, 1982). While the overall incidence of coronary deaths tends to be higher in older persons, the percent of those deaths that are sudden is higher in younger persons (Kannel, et al. 1975; Kannel and Thomas, 1982). For example in the Framingham study, the incidence of coronary death in men ages 45-54 was 1.1/1,000 with 62% sudden, while the incidence in men ages 65-74 was 2.6/1,000 with 42% sudden (Kannel and Thomas, 1982). In Baltimore between 1964-1965, of 322 non-traumatic deaths in young adults (ages 20-39), 31.4% were sudden and unexpected. Sudden, unexpected deaths were more common in blacks and males with alcoholism and fatty liver the leading cause (27.7%). Arteriosclerotic heart disease was the second most common (21.8%) (Kuller, et al., 1966). Lacking in studies that examine causes of sudden, unexpected death are figures that would accurately establish the incidence of sudden death within age groups. Such information is critical to determining whether the incidence of psychotropic drug-related sudden death exceeds that occurring in a comparable, non-drug treated population.

Claims that there was a high incidence of sudden death in New York State in young subjects receiving haloperidol prompted an FDA Advisory Committee meeting in 1980. If one examines the transcript of the Psychopharmacologic Drug Advisory Committee meeting, there is a predominance of deaths in a group under 40 years of age, with women outnumbering men (1980). Since the highest sudden death incidence in the general population appears to be middle-aged males, one wonders if the apparent shift in both age and sex can be accounted for by the drug itself. It would, however, be premature to make such a comparison since totally different population bases would be compared. What is really necessary is the true incidence of sudden death in a population matched in all parameters (age, diagnosis, severity of illness, presence of associated illnesses and other variables) except for the presence of the psychotropic drug. At issue is really whether the incidence of sudden, unexpected natural death is altered by psychotropic drugs. This cannot be established at the moment given available data, and it is a major task to obtain the necessary data with the current data gathering technology for this type of study. However, it is equally true that available data do not exclude the possibility of psychotropic drug induced sudden death.

When psychotropic drug-related sudden deaths were examined in Hungary, it was found that: "The sudden death mortality rate of medicated patients was not higher than that of the general population of the same age distribution" (Ungvari, 1980). Over an 11 year period, 11,935 psychotic patients were treated with neuroleptics. There were eight sudden and unexpected deaths in this population or an incidence of one per 1,492 patients, while in the general population of Hungary , the incidence was one per 1,458 people. The age range of psychotropic drug-related deaths was 21-60 years and the sex distribution ratio was five males to three

females. The age distribution of patients did not differ significantly from that of the general population and the sex distribution was not addressed. Of note was the observation that three out of eight patients were receiving haloperidol alone while two others received haloperidol and phenothiazines. The total number of patients treated with each drug was not given so it is difficult to draw conclusions from these observations.

Even if the incidence of psychotropic drug-related sudden deaths could be shown not to differ from that of a matched, non-drug treated population, it would still be possible that the drugs could increase the risk in some individuals and decrease the risk in others. Since stress, restraint and sudden death may be linked (DeSilva, 1982), it is possible that drugs could reduce the risk of sudden death by calming highly agitated patients, acting as antiarrhythmic agents, or by some other as yet unrecognized mechanism.

Craig and Lin (1981) performed an age-adjusted comparison of populations before and after the use of psychotropic drugs and thus, attempted to define the role of psychotropic drugs in mortality among psychiatric patients. Although they did discuss the apparently high death rate among newly admitted patients (in both periods), the definitional issue of sudden, unexpected, and unexplained was not addressed (and probably could not have been given the data with which they were working). There was no evidence of an increase in mortality after the introduction of drugs and the data actually showed a decline in mortality. Nonetheless, the death rate in hospitalized psychiatric patients remained considerably higher than in the age-matched general population, and the group they found to be at highest risk of death relative to the general population was young women (age 20-29 years). All age and sex groups, however, had a mortality rate that was considerably greater than that of the general population.

The death rate in newly admitted patients, despite a 30% reduction in the drug period, remained quite high. Reasons for this are unclear but may involve factors such as co-existing non-psychiatric medical illness, alcohol, other substance use disorders, and the psychological and physiologic stress of florid psychosis. Since these are the patients in whom psychotropic drugs are likely to be used in high doses and by parenteral administration, it is easy to see how these agents might be etiologically suspected. From an epidemiological point of view, however, this can neither be established nor disproved. The overall reduction in mortality as compared to the pre-drug period could be cited in support of the "life-saving" influences of psychotropic drugs.

To further complicate interpretation of these data, it must be stressed that they were based on mortality rates and did not examine the issue of sudden death. To use them to support or reject an association of psychotropic drugs with sudden, unexpected, natural death would be unwarranted. Definitive mortality statistics from the pre-drug period that focus on sudden, unexpected death with control rather than on overall mortality are not available.

Comparing the incidence of sudden death in psychiatric patients before and after introduction of psychotropic drugs is another method to evaluate a possible relation between sudden death and psychotropic drugs. Although some authors speculate that unexplained, sudden death had increased since the widespread use of psychotropic drugs, an analysis of N. Y. State Hospital data by Brill and Pat ton failed to find such an increase (1962) .

In brief, the epidemiological data do not show an increase of sudden death in patients since the introduction of psychotropic drugs. Since sudden death is not common and almost all psychiatric patients are on medication, it is possible that the role of medication may be coincidental (Wendkos, 1979). The epidemiological data are inadequate to conclude that medication could not be causal in certain situations.

In 1980, the Psychopharmacology Drug Advisory Committee to the FDA addressed the issue of haloperidol associated sudden deaths (1980). Leber posed the following questions which are equally applicable to other individual drugs and to psychotropic drugs as a class:

1. 'What evidence, if any, supports the conclusion that sudden and unexpected death occurs with greater frequency with haloperidol than in other treatments or non-treatments?"

2. "Is there a beyond-chance association between haloperidol and sudden death and, if there is, what evidence implicates haloperidol as the etiologic agent in these sudden deaths, and what is the possible mechanism or mechanisms involved?"

3. "If we do conclude there is a causal risk or causal association, what estimates do we have of its magnitude or significance?"

After reviewing the data, Robinson stated "My conclusion is that it is [an] extremely confusing situation and I think it is very difficult to draw any valid conclusions at this point in time." Stevens concluded "I think we are seeing an unusual unanimity of opinion that adds up that there is a hell of a lot we don't know." The committee ultimately agreed that there were inadequate data available to permit answers to any of the three questions that they addressed.

ANTIARRHYTHMIC EFFECTS OF ANTIPSYCHOTIC DRUGS

Although some have speculated as to sudden death being caused by cardiac effects of these drugs, we note that an opposite case can be made.

Psychotropic drugs may have antiarrhythmic properties in ordinary doses. As early as 1953, Courvioiser and associates reported the ability of chlorpromazine to combat cardiac arrhythmia (1953). The drug, in doses of 2.5 mg/kg intravenously, terminated the arrhythmia induced by succinylcholine in rabbits. In similar doses, it afforded protection against adrenalin-induced arrhythmia in guinea pigs. Chlorpromazine was also found to prevent acetylcholine-induced atrial fibrillation and ether-induced ventricular arrhythmias (Arora, 1956; Melville, 1958). The antiarrhythmic activity of chlorpromazine has been attributed to its central nervous system action, anti-adrenalin effects, quinidine-like property and its local anesthetic action on cardiac cell membrane (Arora, 1979). Similar antiarrhythmic effects have been reported with most psychotropic drugs, including promazine, promethazine, perphenazine, trifluoperazine, levopromazine, prochlorperazine, thioridazine, chlorprothixene, droperidol, reserpine, imipramine, amitriptyline, desipramine, nortriptyline and many antianxiety drugs either in experimental or in clinical studies (Arora, 1956; Reynolds, 1969; Landmark, 1970; Singh, 1970; Baum, 1971; Shamsi, 1971; Szekeres, 1971; Koishnanarao, 1972; Giardina 1979).

CARDIOTOXICITY AND SUDDEN DEATH WITH PSYCHOTROPIC DRUGS

Much attention has been directed towards a possible relation between sudden death and the cardiac effects of psychotropic drugs. Indeed, the action of these drugs on the heart and cardiovascular regulatory mechanism is complex and includes their central and peripheral actions, their effect on adrenergic neurons, cholinergic neurons and receptors (Raisfeld, 1972; Elonon, 1974; Stimmel, 1979a,b).

Asymptomatic electrocardiographic changes such as depression, widening, notching, inversion and flattening of T-waves, presence of U-waves, and prolongation of Q- T intervals have often been reported. Thioridazine is the most frequently reported antipsychotic drug in terms of drug-induced cardiotoxicity and E KG changes. Grauaner and Murphree (1966) noted that on 55 male patients receiving thioridazine in doses of 150-400 mg/day, 68% had electrocardiographic changes, mainly involving the T-wave and S-T segment. Other authors have demonstrated similar electrocardiographic effects following the administration of thioridazine (Huston, 1966; Jean, 1966; Wendkos, 1967). Chlorpromazine seems to have the same effect, but to a lesser extent. Forty patients received chlorpromazine more than 150 mg/day for 7-28 days; 11 developed depression of T-waves and relative increases in Q-T interval (Backman, 1964). Branchey, et al. (1978) compared 30 elderly schizophrenic patients who were treated in a randomized double-blind crossover design with

fluphenazine and thioridazine for eight weeks with four weeks of placebo pre-treatment and prior to the cross-over. There was no difference in therapeutic effects but there were significantly more EKG changes during the thioridazine condition. Branchey found flattening of T-waves in 22 patients receiving thioridazine and one patient on fluphenazine. Twelve subjects had U-wave formation and nine had increased Q-T interval; all patients were on thioridazine. Similar changes have been noted in patients treated with trifluoperazine, mesoridazine, fluphenazine, promazine and thioxanthenes (Ban, 1965; Dillenkoffer et al., 1974a,b; Quitkin, 1976; Stimmel, 1979a,b). Also haloperidol infrequently produces cardiac side effects (Brannan, 1980). Less than 3% of the patients receiving haloperidol developed electrocardiographic changes or other forms of cardiovascular side effects (Goldstein, 1968). There is evidence indicating that these T-wave/S-T segment changes are usually benign: (I) No cardiac symptoms were associated with these findings; (2) the changes were reversible upon discontinuing therapy and they usually reverted to normal within one week after withdrawal of the drug; (3) evidence does not indicate a relationship between these changes and subsequent development of cardiac pathology (Elert, 1969). Furthermore, these changes can be seen in athletes without demonstrable organic heart disease, chronic schizophrenics not receiving any psychotropic medications, and even in physically healthy persons under certain stressful situations (Wendkos, 1964; Hanne-Paparo, 1971; Vincent, 1974). Holden and Itil (1977) reported 196 persons who were studied on placebo therapy. Among them, 57 (290/c) exhibited some form of abnormal electrocardiographic record; the most common being T-wave changes. Thus, the clinical significance of Q-T prolongation, T-wave changes and S-T depression, like other nonspecific ECG abnormalities, is uncertain and requires evaluation in individual patients (Abildskov, 1979),

Although Q-T interval prolongation is often benign, occasional patients develop a life-threatening cardiac arrhythmia called Torsade de Pointes which is characterized by sinus bradycardia with a prolonged Q-T interval, interrupted by runs of ventricular tachycardia that may progress to ventricular fibrillation. Drugs which can cause this syndrome include the Type 1 antiarrhythmic agents (quinidine, procanamide, disopyramide), the tricyclic antidepressants, and the antipsychotic drugs, particularly the phenothiazines and especially thioridazine. The clinical spectrum of manifestations of Torsade de Pointes is quite wide ranging from asymptomatic palpitations to sudden death. A common manifestation is syncope which may be accompanied by myoclonic convulsions due to cerebral ischemia. Treatment of drug-induced Torsade de Pointes consists of discontinuation of the offending agent and treatment of the arrhythmia, either by electrical atrial pacing or with medications, and is best done in a medical intensive care unit. The occurrence of drug-induced Torsade de Pointes in patients taking psychiatric medications is infrequent; however, if it were unnoticed by physicians, deaths due to ventricular arrhythmia could be categorized as unexplained, sudden deaths (Fowler, 1976; Sclarovsky, 1979; Mass. Gen. Newslet. , 1980; Wilson, 1984).

HYPOTENSION

Sudden deaths during psychotropic drug therapy have been attributed to drug-induced hypotension (Rosati, 1964; Leestma and Koening, 1968; Cancro, 1970) from both oral and parenteral medication, the latter route having a higher incidence (Sakalis, 1972). In a group of 515 inpatients maintained on varying doses of chlorpromazine, about 16% showed hypotensive reactions (Szekeres, 1971). Low potency drugs tend to produce hypotension more often (Hirsch, 1971).

Some degree of tolerance is thought to develop to the hypotensive effect within a few days or weeks so that after several weeks of chronic administration of the drugs, blood pressure returns toward normal but complete return to normal does not necessarily occur. How this potential for orthostatic hypotension translates into psychotropic drug-related sudden deaths has not been critically studied. It is possible that such hypotension could be complicated by reduced coronary artery and cerebral perfusion, arrhythmias and an increased risk for sudden death, especially in those such as the elderly who have coexisting cardiovascular disease.

POSTICTAL DEATH

It is well known that patients with seizure disorders are at a slightly increased risk of dying suddenly (Hirsch, 1971; Jay, 1981). Several authors have suggested that sudden death in psychiatric patients receiving psychotropic drugs could be attributed to seizures induced by the obstruction of airway because of glottal spasm or aspiration asphyxia (Zlotlow, 1958; Parks, 1978; Zhang and Zhou, unpublished). However, since seizure or seizure-prone individuals are not uncommon in psychiatric populations, this form of sudden death might happen in patients not receiving psychotropic drugs and has been reported before the introduction of psychotropic drugs.

Antipsychotic drugs have been reported to cause dose related grand mal or focal motor seizures with the incidence of drug-induced seizures less than 1% (Dallos, 1969; Gershon, 1973; Friedlander, 1975; Sovener, 1978). On the other hand, some clinicians note that phenothiazines, butyrophenones and tricyclic antidepressants reduce seizure frequency (Pauig, 1961; Rapoport, 1965; Fromm, 1972). The experimental studies indicate that psychotropic drugs facilitate seizure in animals at low dosage and exert an anticonvulsant effect at high dosage (Friedlander, 1975). The relationship between seizures and psychotropic drugs is unclear at this time, but their potential for increasing seizure frequency in vulnerable subjects must be considered.

ASPIRATION AND ASPHYXIATION

Aspiration with asphyxiation is one of the relatively common causes of sudden death in the psychiatric population as well as in other chronic medical patients (Irwin, 1977) both before 1955 and after. However after 1956, there have been many reports linking sudden death from asphyxiation to the use of psychotropic drugs (Farber, 1957; Feldman, 1957; Hollister, 1957; Wardell, 1957; Childer , 1958; Zlotlow, 1958; Hollister, 1965; Plachta, 1965; Richardson, 1966, Yon Brauchitsch, 1968; Moore, 1969).

Hollister collected 19 cases of unexpected asphyxial deaths at a 1325 bed neuropsychiatric hospital during 1951-1957 (Hollister, 1957). These data represent cases of the pre- and post-psychopharmacotherapy periods in psychiatry. Since 1954, which is the midpoint of this series, the psychotropic drugs were started on a large number of their patients. The report showed this type of death to be no more common during the period of psychotropic drugs than before. Only three patients who died received psychotropic drugs: two chlorpromazine and one prochlorperazine, and in only the former two was the possibility of drug raised as a contributory factor. Richardson and co-workers also made the point that the incidence of asphyxiation in psychiatric patients was no different before and after the use of psychotropic drugs (1966) .

Yon Brauchitsch and May provided meaningful data related to the problem of aspiration in hospitalized patients (1968) .Thirty-five asphyxia cases who died within seconds or a few hours during 1960-1964, comprised 4.2% of all the deaths and were the sixth most frequent cause of death in their institution. They were not able to establish a direct connection between psychotropic medications and deaths from aspiration. There were 16 patients on psychotropic medication: 12 phenothiazines and four minor tranquilizers. Among 12 cases receiving phenothiazines, most of them took a relatively low dosage of drugs such as 300 mg of chlorpromazine or 30 mg of trifluoperazine/day. The risk factors for this form of sudden death were old age, poor dental condition, recent weight loss and acute intercurrent disease.

One of the important factors relating to asphyxiation in psychiatric patients is their eating behavior. Tachyphagia, a special kind of eating behavior, was often found in patients suffering from asphyxiation or aspiration. They were prone to wolf down food without chewing it properly.

This eating habit was also found in some non psychotics and has been noted to be a major cause of sudden death from choking on food, the so-called cafe coronary death (Haugen, 1963).

Some authors believe that psychotropic drugs might interfere with patients' respiratory defense such as impairment of the swallowing or other pharyngeal reflexes, but this has not been conclusively demonstrated (Hussar, 1969). However, there is the possibility that some side effects of antipsychotics such as laryngeal-pharyngeal dystonia could create swallowing difficulties and lead to asphyxia. One might similarly speculate about tardive dyskinesia. Also anticholinergics may make the expression of tardive dyskinesia worse. It has also been suggested that many schizophrenic patients have an absent gag reflex and. therefore, would be vulnerable to swallowing problems. A potentially fatal complication of treatment with antipsychotic medications which can occur quickly is laryngeal spasm or laryngeal/pharyngeal dystonia. In these instances, an acute dystonic reaction may lead to asphyxia and death (Flaherty, 1978; McDanal, 1981; Menuck, 1981, 1985). If recognized promptly, laryngeal/pharyngeal dystonia can be effectively treated with anticholinergic medications. While these may be sudden, they are not unexplained deaths. Methods for diminishing these numbers exist and should be known to administrators and all medical and paramedical personnel involved in the treatment of psychotic states.

MEGACOLON AND PARALYTIC ILEUS

A few reports have been published of sudden death and fatal megacolon or paralytic ileus produced by psychotropic drugs (Burkitt, 1961; Zimmerman, 1962; Milner, 1964, 1966; Warnes, 1967; Giordano, 1975). Consequently, authors have recognized that the incidence of megacolon in psychiatric patients was higher than that in a general population and, therefore, coined the term "megacolon in the insane" (Burrell, 1957). Some authors believe that disturbances of autonomic activity found in some mental patients is also an etiological factor.

Psychotropic drugs might play a precipitating role in the development of fatal or non-fatal megacolon and paralytic ileus. The low-potency antipsychotics and tricyclic antidepressants have anticholinergic activity that is commonly associated with constipation as well as dry mouth and urinary retention. The antiparkinson drugs which are often combined with antipsychotics to relieve extrapyramidal symptoms also have an anticholinergic effect. Anticholinergic-induced inhibition of bowel motility may result in distention developing into megacolon and paralytic ileus (Giordano, 1975). In a survey of chronic mental hospital patients who had received antipsychotic drugs including chlorpromazine, thioridazine and chlorprothixene, dilation of small or large intestine was observed in 12% of autopsy findings with a corresponding figure of 2% in the autopsy findings of medical patients not treated with psychotropic drugs (Zimmerman, 1962). This is an uncommon cause of death and is unlikely to be sudden or unexplained.

HEAT STROKE

Sudden death may occasionally be caused by common heat stroke. Some cases of hyperthermia were associated with overdosage or large doses of psychotropic drugs. For example, three fatal cases of heat stroke were encountered at a Kansas hospital during an oppressive humid heat wave (Ext, 1958) .The potent anti-cholinergic property of some neuroleptics, particularly if combined with anti-parkinson agents, inhibits sweating and cutaneous heat elimination and may be a risk factor in the development of hyperthermia in warm climates. However, impairment of hypothalamic thermoregulation by biogenic amines is probably the major pathogenic mechanism (Baastrup, 1976). In experimental studies, phenothiazine-treated animals placed in low or high environmental temperature are unable to maintain normal body temperature and correspondingly develop hypothermia or hyperthermia (Lomax, 1970).

This has implications for the care of the mentally ill, i.e., that their activities be monitored closely in very hot weather and that adequate temperature control and ventilation be available on wards and rooms, particularly seclusion rooms. In reality, such cases are usually not sudden and can be explained.

MALIGNANT HYPERTHERMIA

Malignant hypenhermia is associated with a genetically determined sensitivity to anesthetics such as halothane (Rosenberg, 1977; Caroff, 1980). The main mechanism is an abnormality in the mobilization of calcium in the muscle leading to a disturbance in muscle contraction that leads to the destruction of muscle fibers (myonecrosis), generation of heat (hyperthermia) and disturbances of cardiac conduction (cardiac arrhythmia). No known cases of malignant hyperthermia have been reported for psychotropic medications.

NEUROLEPTIC MALIGNANT SYNDROME

It is believed that neuroleptics can also cause fever as part of the neuroleptic malignant syndrome (NMS) (Delay and Deniker, 1968; Caroff, 1980), a syndrome of fever and rigidity accompanied more variably by confusion or obtundation, autonomic lability and rhabdomyolysis. All types of neuroleptics have been implicated. Most reported cases resolved after periods of days to weeks, but mortality of 15-20% has been reported. Levinson and Simpson (1986) concluded that in most reported cases of NMS, the primary event may have been severe neuroleptic-induced parkinsonism, causing impairment of eating, walking and/or breathing, with fever following medical complications such as dehydration, myoglobinuria with renal failure, pulmonary embolus and pulmonary infarction. In such cases, disruption of thermoregulation due to central dopamine blockade may interact with the medical disorder to cause fever. These authors suggest that the mortality rate was 8% in those cases without known alternative medical diagnoses, rather than the 15-20% reported previously. Nevertheless, a small number of patients do appear to develop fever coincident with drug-induced parkinsonism in the absence of other medical factors, possibly due to (1) central effects of dopamine blockade on thermoregulation as a primary event, (2) peripheral effects of prolonged muscle contraction on heat production and release of muscle degradation products, and/or (3) a direct effect of neuroleptics on muscle in some patients, similar to the malignant hyperthermia syndrome associated with some anesthetic agents.

While NMS may contribute to some deaths, severe rigidity is usually observed days before any serious medical complications, which occur with or without fever. It would, therefore, appear that interruption of neuroleptic-induced rigidity is critical to the prevention and treatment of complications such as NMS.

PHYSICAL EXHAUSTION

A well-recognized example of sudden death with physical exhaustion is lethal catatonia. Lethal catatonia (Stauder's catatonia, Bell's mania, acute exhaustive mania, malignant or pernicious catatonia) has been reported for more than one hundred years (Bell, 1849). The typical picture is as follows: (I) the main psychiatric syndrome is persistent and extreme psychomotor excitement, often with delusions or hallucinations; (2) continual maniacal furor is followed without any warning by a sudden fatal outcome; (3) the post-mortem examination fails to discover any meaningful anatomical changes. High temperatures and muscular rigidity were also associated with this condition. This syndrome was not uncommon in the first half of this century before the introduction of psychotropic drugs. The cause of death in these patients was usually attributed to cardiovascular collapse produced by physical exhaustion but the role of fluid and electrolyte imbalance was not investigated.

The reports of lethal catatonia have dramatically decreased since the psycho- tropic drugs were introduced suggesting that the successful control of agitated behavior in psychotic patients by these drugs may be related to this decline. Peele and Yon Loetzen (1973) suggest another explanation for the infrequent reports of lethal catatonia, viz., that the histories of so-called phenothiazine death, in recent years, were very similar to that of lethal catatonia. Based on an analysis of reports of sudden death in psychiatric patients, they suggest that most cases of lethal catatonia are now labeled as sudden death related to drugs

OTHER EXPLANATIONS OF SUDDEN APPARENT CARDIAC DEATH

Life events (changes in one's lifestyle or experience) associated with the accumulation of various types of psychological stress such as divorce, bereavement and job loss are known to be associated with sudden cardiac death (Rahe, 1974; Cottington, 1980). Also, the death of a close relative or spouse often precedes sudden cardiac death by up to six months. This period coincides with the period where normal grief is worked out.

Failure to survive a myocardial infarction has been associated with a previous period of dejection, dissatisfaction with achievement and reactive depression. There is also evidence that exertion and fright as well as being awakened by a sudden loud noise can produce sudden death (Wellens, 1972). Giving up in the face of emotional arousal and psychological uncertainty are conditions conducive both to syncope and sudden death. There can also be an activation of the flight-fight and conservation-withdrawal psychophysiological mechanisms during stress that manifest as syncope, dangerous arrhythrmias and sudden death (Engel, 1978). Hlstories of 170 sudden and rapid deaths during acute psychological stress showed helplessness and hopelessness preceding sudden cardiac death (Engel, 1971).

Sudden death may be associated with strenuous exercise. It is well known to occur in young athletes and soldiers (Moritz, 1946; Opie, 1975). Koskenvuo (l976), in an epidemiological survey of conscripts in Finland, found sudden death to be more common among conscripts than among other young men, amounting to one-third of all nonviolent deaths among young conscripts. In more than 30% of the cases, the onset occurred during an estimated near maximum or maximum physical exertion. The highest incidence of sudden death was in the third month of military service at a time when exercise tended to be most strenuous.

Uncontrollable agitation or excitement could sometimes favor the occurrence of sudden death, particularly if the subject remains highly agitated in a room that is inadequately cooled or ventilated. Such an intervention could evoke maladaptive autonomic response which might be followed by an acute cardiac arrest. Several reports describe sudden death before or following the application of restraint (Dimsdale, 1977).

STRESS FACTORS AND SUDDEN DEATH

Stress can be either acute or chronic and its role in sudden cardiac death is indirect. The stress produces a pituitary response, secretion of adrenocorticotropic hormone (ACTH) which leads to the adrenal cortex production of cortisone. Stress also produces an outpouring of epinephrine from the adrenal medulla which may predispose to ventricular fibrillation and sudden cardiac death (Lown, 1973). There is evidence in patients with coronary disease that acute psychological stress is more likely to result in instantaneous or rapid death from ventricular fibrillation without the evolution of acute myocardial infarction. In prolonged chronic stress, the chances of acute myocardial infarction are more common (Rissanen, 1978). Intense emotions such as anger, fear and excitement related to situational stress are known to trigger malignant arrhythmias in high-risk groups of patients (Myers, 1975).

Studies on the prevalence of psychological stress during a 24-hour period preceding life-threatening ventricular arrhythmias have shown that about 25% of these patients have experienced acute emotional disturbances. These reactions to emotional stress have been associated with type A behavior and depression (Bruhn, 1984). Acute occurrence of arousal states, psychological or social stresses during an ongoing depression are also known to be common precursors of sudden death (Greene, 1972). Other indirect evidence that psychosocial stress is associated with sudden cardiac death is the high incidence of such death on Mondays, i.e., reintroduction to occupational stress and exposure to other social-related stresses (Rabkin, 1980).

Current evidence supports the role of higher nervous activity which is influenced by stress as a major contributor to destabilization of normal cardiac rhythm and to sudden cardiac death. Ventricular premature beats and E KG changes may be evoked by the psychological stress of emotional problems. Paroxysms of ventricular tachycardia and S-T segment and T-wave abnormalities were noted during interviews conducted with patients undergoing severe emotional stress (Rubin, 1966; DeSilva and Lown, 1978).

Sympathetic and cholinergic factors are involved in stress-induced cardiovascular changes (Benedict, 1952; Sigler, 1961; Groover, 1966; Selye. 1970; Keegan, 1973; Taggart, 1973; Reder, 1978; Lown, 1980). Stressful situations increase serum catecholamine levels up to 20 times greater than normal.

There is an overwhelming literature showing that abnormal cardiac events such as arrhythmias and disorders of conduction can occur without evidence of symptoms of cardiac disease (Grossman, 1958; Johnson, 1960; Hinkle, 1969; Dolara, 1970), or with cardiac symptoms but no cardiac pathology (Spaulding, 1977), or in those who died suddenly but show no evidence of coronary artery disease, myocardial damage or other organ pathology (Cobb, 1975; Newman. 1982). Research findings also support the notion that CNS and conditioning factors can playa significant role in sudden cardiac death. Further Pavlovian conditioning factors have been shown in preliminary studies to be of importance in sudden death (Gantt, 1940; Notterman, 1952; Perez-Cruet, 1962; 1973; Lee. et al., 1973; Lown, 1973; Malta, 1976; DeSilva, et al., 1978)

CONCLUSIONS

While there are plenty of explanations as to why sudden death might occur in a psychiatric population, the studies in Hungary, U.S.A. and China show no evidence for an increase in sudden death in patients receiving psychotropic medications. This does not mean, however, that the question of a relationship between the administration of psychotropic agents and sudden death has been answered.

We are left with the following conclusions. Sudden, unexplained death that takes place in the general population is often associated with stress and frequently accompanied by negative autopsy findings.

Death among psychiatric inpatients has decreased since the introduction of psychotropic drugs but is still higher than in the general population. Sudden death has not increased since the introduction of psychotropic drugs. Independent studies from three different countries find no differences in mortality in patients given antipsychotic agents compared to the general population. When sudden death occurs in an understaffed psychiatric hospital, the nagging doubt remains that something lacking in quality of care might have contributed. We further note that chronic psychiatric hospitals have become the repositories of an aberrant group of acute and chronic patients who are, in some way, treatment-resistant and might be expected to exhibit more violent and disruptive behavior. Many of the patients seem to have disrupted cognitive function. Other mental illness is complicated by low IQ, alcoholism, drug dependence and physical illness.

All of these could be risk factors for cardiac illness. If they were merely chronically hallucinating and responsive to psychotropic medications, they could be in the community. Patients with violent outbursts against self and others may also receive high doses of psychotropic drugs in an attempt to control these behaviors. Currently, there is little evidence to support the

efficacy of such treatment and this is an area that needs to be researched since there is an urgent need to try to separate out some of the factors in this situation.

All hospitals with psychiatric beds should have a protocol for investigating all cases of sudden, unexpected deaths. One provision of such policy should be the encouragement of an autopsy which would include microscopic examination of the conduction pathways and coronary vasculature of the heart.

As mentioned earlier, it is conceivable that antipsychotic agents could cause sudden death in some subjects but prevent it in others. Thus, acutely excited psychotic patients may require considerable amounts of antipsychotic agents which, if all works out well, may reduce psychotic symptoms and reduce vulnerability to stressful reactions (including sudden death). On the other hand, it is possible that the pharmacological actions of the drug could interact with the stress to make the subject more vulnerable to cardiac arrhythmias and autonomic system complications. In that case, the amount of the psychotropic agent given could be a factor. Although, there are no data on this subject, a dose-response relationship might be predicted. Efforts to minimize the amount the neuroleptic used to treat psychotic inpatients involve factors such as the milieu of the institution, i.e., the relationship of the staff, the staffing patterns, academic standards, ethics and morale.

Similarly, the amount of restraint used depends not only on the acuteness or dangerousness of psychotic behavior but also on the ability of the ward staff to handle such problems. Thus, if we consider restraint as an undesirable procedure that is sometimes necessary in treating psychotic inpatients, it may be necessary to reevaluate the best way to carry this out. This is emphasized since there is a notion that agitated patients in restraint or seclusion are, perhaps, more vulnerable to hyperpyrexia and sudden death. Given that restraint or seclusion is a treatment reserved for the most uncontrolled excitable patients, then clearly such patients are already at risk. However, a re-examination of the use of restraints and types of restraints may be in order. Restraint orders must be issued by a physician after seeing the patient and patients should be closely monitored by nurses and paramedical staff. Case conferences should be held to discuss and focus on restraint (APA Task Force Report, 1985).

Two other conditions which have been recently associated with sudden death, namely heat stroke and the neuroleptic malignant syndrome, could be discussed in this context although, as a rule, neither are sudden or cause death of unknown cause. Heat stroke does occur in hot weather, in overexercised, overweight, underfit, nonpychotic subjects overexposed to the sun. Neuroleptics, by their effect on temperature control systems, alter the physiology of hypothalamic thermoregulation and peripheral mechanisms of heat exchange. Therefore, subjects may be more at risk to extremes of ambient temperature. It is for this reason that patients on neuroleptics may develop hyperpyrexia in warm climates and hypothermia in cold climates. There is, therefore, a need to pay attention to temperature charting in the medical record, particularly in susceptible subjects who may be in restraint or seclusion rooms.

Although a relationship between the use of antipsychotic drugs and sudden death has not been firmly established, it also has not been disproven. From a neurocardiologic perspective, these drugs have the potential for both increasing and decreasing the risk of sudden death. Ultimate outcome is probably determined by a multitude of interacting factors, and the role played by the drug in a given individual is difficult, if not impossible, to determine.

RECOMMENDATIONS

The properly designed epidemiological studies that might determine the role of these drugs in sudden death have not been done and are probably not possible because of logistical and financial considerations. The possibility of a large scale comparison of different treatment regimens, e.g., low doses of neuroleptics + benzodiazepines vs. conventional neuroleptics could possibly be considered. If severe or life-threatening events were prospectively operationalized and defined, it is possible that the question of dosage as a variable could be addressed, e.g., in the above study, comparison of a low dose of a neuroleptic treatment vs. routine or high dose neuroleptic treatment. While this would require a huge sample size and is perhaps a bit speculative, nonetheless, it may be worth considering. In the meantime, it should be stressed that sudden death occurs in all populations, psychiatric and non-psychiatric, medicated and unmedicated. To reduce the risk to zero in any population is idealistic but unrealistic and impossible. To minimize risk is certainly a desirable goal.

A certain number of drug-related deaths may be unavoidable even when the drugs are used correctly for appropriate indications. Koch-Weser wisely states: "When life-threatening diseases are treated with potent drugs, the net result of therapy in a few patients will inevitably be negative. Few drugs that help anybody will not hurt somebody, and all potent drugs, no matter how skillfully used, can cause serious untoward effects in some patients. The naive demand for 'completely safe' drugs is a pharmacologic absurdity." This is not to deny that lethal drug reactions may also be the result of "inappropriate or unskilled pharmacotherapy" (Koch-Weser, 1974).

To better understand the possible relationships between antipsychotic drugs and sudden death, there is a need for a system that would operate nation-wide using thorough and standardized data collecting techniques. A National Clearinghouse for Sudden Death in Psychiatric Patients could be established with regional centers to gather and process information similar to Drug Information and Poison Control Centers. These regional centers would be linked at one end to hospitals and outpatient settings and at the other to the central headquarters. The problem of reporting bias would remain, but this or a more extensive use of the current system is needed.

Since sudden, unexplained death in psychiatric patients receiving antipsychotic drugs is a rare, unpredictable event, specific risk factors have not been clearly identified. Nonetheless, certain recommendations can be made both with regard to prevention and treatment. Efforts should be made to use the lowest effective doses of antipsychotic drugs. The evidence that "rapid tranquilization" with frequent parenteral administration of substantial amounts of drugs has a better outcome than a more conservative approach is not convincing. Preliminary studies using benzodiazepines to compliment antipsychotics in the acute phases of treatment are promising in that lower doses of the latter are possible. A further area of research is the development of alternatives to antipsychotic drugs for quieting acutely excited patients. Conventional antipsychotic agents can produce akathisia which is difficult to diagnose in acutely excited patients. Thus, it may not be clear that the treatment given is exacerbating the condition. Low doses of high potency neuroleptics given orally rather than parenterally could be helpful. Studies of agents that do not produce akathisia would be useful. These agents could at least be interspersed with injections of low doses of neuroleptics, Sodium amytal, benzodiazepines or some type of modified sleep treatment could be explored. The use of ECT in situations such as this could also be fully evaluated. All of these are alternative treatments; however, they also carry the risk of sudden death and other medical complications.

Treatment setting and staff can also have a marked influence on how quickly and effectively agitated, psychotic behavior is controlled. A well-trained staff in a quiet, comfortable, well-ventilated, temperature controlled setting will result in a reduction in the amount of antipsychotic drug needed to control behavior .

Training in cardiopulmonary resuscitation (CPR) should be mandatory for hospital staff (doctors, nurses, students, aids) with both certification and periodic recertification a requirement. In addition, resuscitation equipment should be immediately available. Practice drills should be incorporated into staff training programs to prepare staff to act swiftly and appropriately should a real emergency occur.

Given the tendency for many patients to rapidly eat inadequately chewed food, and the possible blunted or absent gag reflex in some patients, attention should be paid to providing sufficient time to eat and to

training in proper eating habits. Staff should be familiar with the Heimlich maneuver and other anti-choking techniques.

When dealing with acutely ill, high risk patients receiving frequent and often generous doses of antipsychotic drugs, regular monitoring of vital signs is es- sential (including temperature, pulse and postural blood pressure). Early detection of fever will allow prompt recognition of neuroleptic malignant syndrome. The NMS is a syndrome that includes hyperpyrexia, catatonia and extrapyramidal effects. It has become a frequently-made diagnosis but no precise criteria for making the diagnosis are in routine use. It is emphasized that attention be paid to environment and temperature charting as mentioned above. In situations with acute, excited patients when it is temporarily impossible to carry out a reasonable physical examination and laboratory work up, the patient's temperature should be taken if only by use of a tape thermometer which can be placed on the brow even though the readings are not as accurate as an oral thermometer measurement. This will permit treatment at a time most likely to be effective. The appropriate temperature lowering techniques should be readily available and staff trained in their use.

High risk patients should receive frequent and regular "eyes on" evaluation with required documentation that contact has been made (e.g., signature sheet on patient's door). Unless video monitoring is available, this is the only way to insure that untoward events will be detected in a fashion timely enough to offer the potential for successful intervention.

In general, much can be done to improve the overall quality of patient care. It makes intuitive sense that some of these measures may also reduce the risk of sudden death in psychiatric patients. At the same time, it is important to remember that perfection is not an attainable goal and that some morbidity and mortality is a necessary consequence of treating people with serious illnesses. Our task is to reduce risk to a level that is realistically attainable, utilizing the best available standards of patient care.

If a balanced perspective is not maintained, it is all too tempting to conclude that any sudden death occurring in the presence of an antipsychotic drug is due to the drug, and that any sudden death occurring in a drug-free patient could have been prevented by the use of a drug.

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