

Struggles in prescribing:

determinants of psychotropic drug use in multiple clinical settings

Joost Jan Stolker

Cover illustration: Bas Sebus, 'Ecstasy', oil on canvas, 80 x 60 cm, 2002

The picture was specially made by me for this book. It is the direct result of an one hour brainstorm session that Joost Jan and I had on February 19th of this year. I had an idea to start with but Joost Jan wanted pills and aggression. So the wild horse came from me. (I had no pictures of rodeo in my studio, but the internet is a good catalogue). And so the picture grew into its present shape. A man who tries to drive an excited horse with his feet in a flood of high velocity pills.

Bas Sebus

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determinants of psychotropic drug use in multiple clinical settings

Dilemma's bij het voorschrijven:
determinanten van gebruik van psychofarmaca in
verschillende klinische populaties

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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Voor mijn ouders, Teun en Riet

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CHAPTER 1

Introduction

1.1 Scope of the thesis

1.2 Pharmacoepidemiological research in psychiatry

CHAPTER 1.1

Scope of the thesis

INTRODUCTION

The year 1952 is generally seen as the start of modern psychopharmacology with the introduction of the antipsychotic drugs, chlorpromazine and reserpine [1-3]. That year also saw the publication of the first reports of the anti-depressive effect of iproniazid, a monoamine oxidase inhibitor (MAOI) derived from isoniazid and a known tuberculostaticum [1-3]. The prescribing of psychotropic drugs has since gained ample attention and during the 'golden age of drug discovery' of the 1950s and early 1960s, there was an overwhelming optimism about the therapeutic possibilities to treat mentally ill patients. The first randomised-controlled trials with chlorpromazine, iproniazid and later phenelzine were conducted during this period [1]. Many new psychotropic compounds followed these first discoveries into clinical practice, although from today's standards, their therapeutic effectiveness and safety were far from ideal. This thesis presents studies on psychotropic drug prescribing. In the introduction, we will explore the changes in the scientific aspects and practice of drug development that have impacted the prescribing of psychotropic drugs.

DISCOVERY, DEVELOPMENT AND INDICATIONS OF PSYCHOTROPIC DRUGS

The process of discovery and development of drugs has changed dramatically over the last decades [4]. The current application to register a psychotropic drug for a specific indication is very stringent. Previously, drugs could be registered for a variety of indications without thorough evaluation and examples of such practice can still be found in the Dutch Repertorium of Medicines [5]. Thioridazine was registered first in 1967 for use in patients with psychotic disorders (Melleril®) and later in 1979 for use in low dosages in patients with neurotic depressions (Melleretten®). In the 1960s, several classical antipsychotic drugs, including haloperidol and zuclopenthixol, were registered for two indications, for psychotic disorders and agitation. In contrast, recently registered atypical antipsychotic drugs, risperidone, olanzapine and quetiapine, are only licensed for schizophrenia.

The indications for the first psychotropic agents were discovered by serendipity. Initial observations of patients suffering from tuberculosis treated with

iproniazid noted 'euphoric' effects and, subsequently, it was successfully tried in patients with depression [1-3]. Imipramine was developed as an antipsychotic because of its similarity to chlorpromazine [1-3], but it was found to be ineffective in schizophrenic patients and in some cases, it caused manic feelings. Imipramine was later found to be more beneficial as an antidepressant [6].

Following registration, many psychotropic drugs were assessed in different patient groups in various settings. In 'Psychofarmacotherapie' [7], Börger and Weijling suggested a broader spectrum of indications for psychotropics based mostly on their own experiences, case reports in literature and open studies. For example, chlorpromazine, diazepam, sulpiride, trifluoperidol and flupenthixol were proposed for the treatment of anorexia nervosa; chlorpromazine, levomepromazine, sulpiride and clorazepate were proposed for the treatment of behavioural disorders in 'oligophrenia'. Although, none of these recommendations were based on the results from randomised controlled trials (RCTs), 'Psychofarmacotherapie' has served as a basis for psychotropic drug prescribing in the Netherlands for many years.

Since the 1970s and 1980s, the results of RCTs have provided evidence for the efficacy of specific drugs for a particular indication. Liebowitz et al [8] found that MAOI phenelzine was superior to imipramine for treating patients with atypical depression. Nolen et al [9] reported that the MAOI tranylcypromine was effective in depressed patients resistant to tricyclic antidepressants. Similarly, Kane et al [10] found that clozapine was superior to chlorpromazine in schizophrenic patients resistant to regular antipsychotics.

Psychotropics are also widely used for unregistered indications of use. Such off-label use may be risky because the balance between safety and efficacy has not been carefully studied [11]. Different types of off-label prescription can be distinguished. For example, some Selective Serotonin Reuptake Inhibitors (SSRIs) registered for depressive disorders, are unregistered for other indications such as obsessive-compulsive disorders but are prescribed for this purpose because other SSRIs are registered for this indication. It is also possible that registered psychotropics are prescribed for indications without a licensed

drug, such as SSRIs being prescribed in patients with borderline personality disorders. Another type of off-label prescription is the use of non-registered psychotropics: for example, tranylcypromine is widely used in the Netherlands to treat resistant depressive disorders and only available as a so-called 'orphan drug'. Furthermore, patients informed by the media and internet may ask their physician to prescribe an agent which is not well studied [11]. Physicians may feel pressure to prescribe psychotropics to treat some disorders, despite the lack of evidence from RCTs to support their use [12, 13]. Antidepressants, as an example, are frequently used in bipolar depression. In contrast to the many hundreds of RCTs studying major depression, only ten RCTs have been conducted in bipolar depression [14]. The efficacy of an antidepressant compared to placebo still remains to be proven.

CHANGES IN THE PRACTICE OF PSYCHIATRY

In the 1950s and 1960s, diagnosis did not have a high priority in psychiatry and terms like 'schizophrenia' varied in meaning across different countries [15]. After a long period of psychoanalytic dominance, however, the importance of psychiatric diagnosis was consolidated as a consequence of the flourishing of biological psychiatry [16]. In the 1970s, the 'Feighner Criteria' [17] and the Research Diagnostic Criteria [18] were developed resulting in a revision of the Diagnostic and Statistic Manual of mental disorders: DSM-III [19]. It then became possible to classify diagnoses according to strict criteria which, subsequently, boosted scientific research [16]. Partly motivated by fear of a too rigid scientific approach and as a reaction to a strong belief in biological treatment methods, biological psychiatry and psychopharmacotherapy became the target of criticism from the late 1960s to the early 1980s [16]. Many argued that mental disease was a 'product' of social, cultural or political suffering, and there was a strong drift away from 'biology' as model to understand and approach mental illness [16]. The term 'antipsychiatry' was coined during this era. The erratic prescribing of benzodiazepines, in particular, was extensively studied and debated [20-23]. Controversies arose about the safety of these psychotropic drugs in terms of dependence risk, falls, accidents, and 'medicalisation' of underlying psychological and social problems. Thus, the climate was not very favourable for the pharmaceutical industry to invest in the development of psychotropic drugs. This all changed in the late 1980s and

1990s when rational drug design, evaluation and prescribing became dominant models of thought. Although, psychiatry is frequently confronted with difficulties in understanding aetiology, diagnosis and establishment of targets for treatment, significant progress has been made to rationalise and give it a scientific foundation. It has become progressively more biological over the last decades and less conceptually isolated from the rest of medicine [24, 25].

EVIDENCE-BASED MEDICINE

In the climate of scientific, rational and biological psychiatry, evidence-based medicine (EBM), defined as the 'conscientious, explicit and judicious use of the best evidence in making decisions about the care of individual patients' became important to the current view on mental health care [26, 27]. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research. In the view of EBM, when deciding on therapy, non-experimental approaches should be avoided as these routinely lead to false positive conclusions about efficacy. To provide evidence-based health care, compendia of systematic summaries of evidence-based interventions such as the Cochrane Library, have been developed [28]. The aim is to prepare, maintain and promote the accessibility of systematic reviews on the effects of health care interventions [29]. However, the emphasis of EBM on the assumption that medical interventions can always be rational and measurable has been criticised. Faulkner and Thomas [30] mention that: 'clinical effectiveness, if restricted to the narrow definition of 'symptom relief', may fail to take into account relevant aspects of people's lives, aspects that may be crucial in determining an individual's decision to continue treatment, remain in contact with services or indeed survive'. Too great an emphasis on EBM oversimplifies the complex and interpersonal nature of clinical care and does not take into account the contribution of the physician's personality and attitude to the outcome [31, 32]. Patients may feel that their concerns are forgotten and they are not much more than a disease being treated [30].

THE NON-PHARMACOLOGICAL 'CULTURE' OF PSYCHOTROPIC DRUG PRESCRIBING

There has been an increasing demand for the treatment of patients with psychiatric disorders [33]. With an aging population, the risk of mental disorders, such as dementia, increases [34]. Our society has become 'multicultural' which has also an effect on the prevalence of psychiatric disorders such as schizophrenia [35]. A recent population study has found psychiatric disorders to be very common in the Netherlands: the lifetime prevalence of all disorders was 41.2%; the 12-month prevalence was 23.5%. Depression, anxiety disorders, alcohol abuse and dependence were reported to have high prevalence and high co-morbidity [36]. Of those 23.5% who reported having one or more psychiatric disorders in the past year, 33.9% sought some form of professional care [37]. Various demographic characteristics were associated with individuals seeking treatment. People with mood disorders were most likely to use professional care and those with alcohol- or drug-related disorders were least likely to do so. Higher educated single persons, single parents, unemployed persons, and disabled persons were more likely to use mental health care [37].

Despite the high prevalence of psychiatric disorders, Netherlands' general practice has the lowest number of prescribed drugs per confirmed diagnosis among European countries [38]. Nevertheless, there is pressure on physicians to prescribe psychotropics more often. Additionally, there is a shortage of beds for severely disturbed patients and patients are discharged from admission wards sooner than before [39]. Furthermore, in our 'poldermodel' culture [40], patients and family members informed by the media, internet, patient or family associations frequently pressure the physician into prescribing psychotropic drugs. Nurses, caring for a patient and facing his or her problems for many hours a day, can also sometimes urge the physician to prescribe medications.

National differences related to cultural values exist in the use of psychotropics within Europe. Compared to other European countries, the Netherlands has low consumption and costs of medicines [41]. However, use of psychotropic drugs expressed in number of prescriptions increases. For example, the use of antidepressants from 1999 to 2001 increased by 17% in the Netherlands, as

compared to 22% and 2.5% in Spain and Germany, respectively (IMS Health BV, personal communication, 2002). Germany uses significantly less tranquillisers and more herbal remedies than the rest of Europe [42, 43].

Regional differences in the use of psychotropics exist within the Netherlands. Egberts et al [44] found that although the same five antidepressant drugs, namely amitriptyline, clomipramine, fluoxetine, fluvoxamine and paroxetine, were among the most frequent first prescriptions, the ranking of these drugs differed between the northern and southern regions of the country. The process of prescribing an antidepressant drug for first time users was influenced primarily by regional preferences and less determined by patients characteristics, such as gender and prescriber (general practitioner or specialist). These variations likely pertain to different regional guidelines for the use of psychotropics and to promotional activities of pharmaceutical industries.

Good health and belief in the autonomy of the patient are important values in the Western world [45]. Patients demand to be informed about their medicines by their physician and pharmacist [46]. Information on psychotropic drugs and psychiatric disorders is easily accessible from the media, internet and patient societies, and personal experiences of psychiatric disorders are publicly expressed. It is generally known that Prince Claus, Queen Beatrix's husband, suffers from a depressive disorder. The Dutch psychiatrist Prof P.C. Kuiper wrote a book about his own depression [47]. The British Princess of Wales, Diana spoke about her eating disorder in a television interview, and the Dutch newspaper columnist, Emma Brunt, reported on her own depression and its successful treatment with antidepressants after years of psychotherapy [48].

Alongside this celebrity openness, the 1990s hype of the antidepressant Prozac was another factor contributing to the de-stigmatisation of psychiatric disorders [16]. Kramer [49] coined the term 'cosmetic psychopharmacology' in his book 'Listening to Prozac'. He suggested that SSRIs may be used to improve personality traits in normal individuals, without a formal psychiatric diagnosis. 'Cosmetic psychopharmacology' may lead people not suffering from psychiatric disorders but from normal unpleasant feelings of anxiety and dysphoria to seek to relief from their problems with psychotropics, like fluoxetine (Prozac®) and

see their physician as supplier of drugs [16]. Kramer's book has been criticised but it also inspired researchers to think seriously about issues, such as the relationship between personality and depression [50].

OBJECTIVES OF THE THESIS

The reality of clinical practice may appear to be 'at odds' with official registrations and the results from RCTs. Studying determinants of psychotropic drug use may help to explore the gap between clinical practice and evidence. The primary objectives of this thesis are to assess the prevalence of psychotropic drug use and analyse possible determinants associated with its use in four clinical settings. The four settings are characterised by a heterogeneous population of patients with psychiatric and somatic comorbidity. In the admission wards, nearly all hospitalisations are acute, and many patients are involuntarily admitted. In the intensive care settings, comorbid (organic) psychiatric disorders are frequently seen in somatically ill patients with severe internal diseases or in those following surgical interventions. In the homes for the intellectually disabled, behavioural problems occur frequently. In the specialised psychiatric unit for intellectually disabled, only severely ill patients who cannot be treated elsewhere are hospitalised here as a last resort.

In the following section of the introduction (Chapter 1.2), we highlight methods used in pharmacoepidemiology, consider differences between randomised controlled trials and observational research, and discuss possibilities and limitations of these methods in psychiatric research.

Chapters 2, 3 and 4 present the empirical findings of this thesis. In Chapter 2.1, we investigate the selection of antipsychotic drugs (classical versus atypical) prescribed in a psychiatric hospital. Factors associated with choosing between the two classes of antipsychotics for the treatment of newly admitted patients on acute psychiatric wards are explored. In Chapter 2.2, the results of a study on the association between antipsychotics and seclusion are presented. Chapter 3.1 focuses on the association between patient-related factors and psychotropic drug use in an intensive care unit for somatically ill patients. In Chapter 3.2, the methods used in the intensive care study are first examined

and then compared to different study designs. Chapter 4 reports on the analyses on the use of psychotropic drug in a population of intellectually disabled patients. In Chapter 4.1, results of a study on psychotropic drug use among residents of group homes with behavioural problems compared to a randomly selected group of residents are presented. In Chapter 4.2, determinants of multiple drug use are studied at a specialised unit of a psychiatric hospital. A discussion of all our studies, with implications for research and clinical practice, is presented in Chapter 5. Chapter 6 provides a summary of this thesis.

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CHAPTER 1.2

Pharmacoepidemiological research in psychiatry

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ABSTRACT

Because of the strict in- and exclusion criteria applied in randomised controlled trials (RCTs), the populations participating in RCTs differs greatly from daily practice and therefore effectiveness of a drug in daily practice can only be limitedly predicted. Pharmacoepidemiological research is very helpful to get additional information. In this Chapter we discuss the methods used in pharmacoepidemiology, consider the differences between randomised controlled trials and observational research and discuss the possibilities and weaknesses of pharmacoepidemiological research in psychiatry. Pharmacoepidemiology makes it possible to get additional insights into effectiveness and safety of psychotropics in clinical practice.

INTRODUCTION

Psychiatry has gone through major changes during the second half of the last century, mainly due to the advent of psychopharmacology. The increasing number of patients on psychotropics can be investigated through pharmaco-epidemiological research, in which patterns of use and the effects of the drugs, both adverse and beneficiary, may be studied in daily practice.

In this Chapter we will discuss the methodology of this type of research, consider the differences between the randomised controlled trial (RCT) and observational research and discuss the possibilities and weaknesses of pharmacoepidemiological research in psychiatry. We will illustrate this through a number of studies that will be presented throughout the Chapter.

WHAT IS PHARMACOEPIDEMOLOGY?

In 1961, the New Zealand physician McBride published a letter in *The Lancet* in which he reported his observation that an unexpectedly large number of congenital abnormalities were found in children from mothers that had used the hypnotic thalidomide [1]. Until then this drug had been promoted as a safe alternative to the barbiturates. McBride's publication can be seen as a breakthrough in the thinking about the need for continuous evaluation of quality, effectiveness and safety of drugs after marketing. While (pharmacological) efficacy and safety of a drug must be proven before its registration, very little is known on the use, effectiveness and safety of a drug in daily clinical practice at the time of registration. In 1984, Lawson coined the term pharmacoepidemiology for the science that bridges clinical pharmacology and epidemiology [2]. Pharmacoepidemiology studies the use and the effects of drugs in large populations, including determinants of use while its most important characteristic is its observational nature in which it fundamentally differs from pre-registration RCTs.

OBSERVATIONAL RESEARCH AND RANDOMISED CLINICAL RESEARCH

For registration purposes, the RCT is considered to be the 'Golden Standard'. In an RCT, relatively few carefully selected patients are randomly assigned to an experimental group and to one or more control groups. Limited conclusions on

the effects of drugs in daily practice can be drawn from the results of such RCTs. Through selection of patients for RCTs large discrepancies arise between the populations participating in a RCT and those who are prescribed the drug directly following marketing [3]. Participants in RCTs are more often young, male, have a less severe disease status and less co-morbidity and co-medication and show a better therapy compliance compared to patients in daily practice [3]. Moreover, newly registered drugs have to compete with existing drugs for similar indications. This may result in a marked selection of patients to whom new drugs are prescribed, e.g. patients who are therapy resistant or who have experienced adverse effects with previous therapy.

Large scale observational studies offer better generalisability of results into daily clinical practice. The major disadvantage is that treatments are not randomised, which may influence the comparison between drugs resulting in differences in outcomes that are inadvertently attributed to the use of a certain drug. This is illustrated in a study in which 228 psychiatrists and general physicians filled in a questionnaire on indications of antidepressants [4]. It was found that clomipramine and amitriptyline were most often prescribed for major depression and other diseases including anxiety disorders and pain. Antidepressants with a known lower toxicity in overdose (such as moclobemide) were more often prescribed to patients with suicidal tendencies. If this is not taken into account in pharmacoepidemiological analysis, this could lead to the (most likely incorrect) conclusion that there is an association between moclobemide and suicide.

APPLICATIONS OF PHARMACOEPIDEMOLOGICAL RESEARCH

Evaluation of (un)known adverse effects

In Table 1 the most important applications of pharmacoepidemiological research are listed. Adverse events are often not detected in the relatively small and highly selected populations included in RCTs, especially when the adverse event is rare and/or occurs only after long term use. This is why registration authorities request physicians and pharmacists to report unknown and serious adverse events of marketed drugs. In most European countries these spontaneous adverse drug reaction reporting systems are based on voluntary action. A recent example of the evidence from spontaneous reporting systems

are the reports from the Swedish Adverse Reactions Advisory Committee suggesting that clozapine is associated with venous thromboembolic complications [5, 6]. In another example, cases of non-puerperal lactation associated with antidepressant drug use reported to a spontaneous adverse drug reaction programme in the Netherlands were evaluated [7].

Table 1. Applications of pharmacoepidemiological research -adapted from Strom- [8].

More insight in:

- (Un)known adverse effects
 - in a normal population
 - in a population not studied prior to marketing (elderly, children, pregnant women, patients with comorbidity, non-compliant patients, etc.)
 - in cases of drug overdoses
 - in cases of drug interactions
 - The use of drugs in daily practice
 - Characteristics of a drug compared to other drugs with a similar indication
 - Pharmaco-economic aspects
-

Post marketing surveillance (PMS) is a form of pharmacoepidemiological research defined as the monitoring of and scientific study into all adverse and beneficiary effects of marketed drugs. PMS studies have been widely criticised [9-12]. When sponsored and conducted by pharmaceutical industry, they are sometimes misused for marketing purposes. A British group of academic researchers, government, and pharmaceutical industry have developed guidelines for the Safety Assessments of Marketed Medicines (SAMM guidelines) listed in Table 2 [13].

Besides government and pharmaceutical industry, clinicians are interested in differences in effects of drugs in daily practice. This is illustrated by a recent study conducted in a population of 39,807 antidepressant users identified in a prescription database in Denmark [14]. Users of tricyclic antidepressants had an excess of non-Hodgkin's lymphoma, with the risk increasing with the number of prescriptions of tricyclic antidepressants. The standardised incidence ratio was 2.5 (95% confidence interval: 1.4-4.2) for those with five or more prescriptions.

Table 2. Safety of Marketed Medicines (SAMM) guidelines [12].

-
- The research population must be as representative as possible of the general population of users.
 - The prescribing of a drug and the inclusion of the patient in a study are two issues which must be clearly separated. The drug should be prescribed in the usual manner.
 - An appropriate comparator group must be included.
 - Patients must not be prescribed particular medication in order to include them in a study.
 - The number of patients to be entered by a single doctor is limited. No patient should be entered into more than one study simultaneously.
 - The study should not be conducted for the purposes of promotion.
 - The doctor receives only payment in recompense for his time and any expenses incurred.
-

The use of drugs in daily practice

Drug utilisation in daily practice is exemplified by a study into the actual use of antidepressants [15]. Prescribing patterns of antidepressants were analysed using data of insurance claims. It was shown that over 50% of the patients used antidepressants for fewer than 4 months. Also, the average daily dosages were significantly lower than the recommended dosages in depression. The conclusion of this study was that a substantial part of patients was not adequately treated.

For large scale observational studies it is important to establish large databases containing information on drug use. During the last decades, a number of these databases linking drug prescription data to clinical data have been developed with their own individual strengths and weaknesses. For example, in the USA data of the Kaiser Permanente Medical Care Program are used for pharmacoepidemiological studies [16]. In Canada, the Saskatchewan Health Databases have been developed and in the UK the Tayside Medicines Monitoring Unit [17, 18]. In the Netherlands, the PHARMO database system was been used for research purposes since the early nineties [19]. For example, in a study into benzodiazepines and the risk of falling leading to femur fractures among patients of 55 years or older, this database was used [20]. It

was seen that the use of benzodiazepines is an important risk factor for falls leading to these fractures probably explained by prescribing too high doses.

Characteristics of a drug compared to other drugs with a similar indication

When a drug is newly registered, one wants to know how the effects of the drug in daily practice compares to drugs that are already available for the same indication. In pharmacoepidemiological research patients on a certain drug may be compared to patients on another drug for the same indication. Various outcomes that can be studied include safety aspects (the occurrence of adverse effects, the use of co-medication for the treatment of possible adverse effects and hospitalisations), effectiveness (reduction of symptoms, duration of use and recurrence of disease) and drug utilisation/prescribing patterns (patient questionnaires, ease of use and compliance). For example, in a recent study the prescribing of TCAs versus SSRIs in elderly patients was evaluated through measurement of adverse effects and the severity of depressive disorder [21].

Pharmacoeconomic aspects

During the last years, pharmacoeconomic aspects in prescribing have become more and more important. Many studies into these aspects are based on RCTs with a retrospective calculation of the costs in which determinants are associated with the use of the drug [22, 23]. These methods have serious limitations in their applicability to real-life data [24].

An example of a pharmacoeconomic study not using data of an RCT is a study into the 1-year total direct health care costs for patients initiating therapy with TCAs compared with SSRIs [25]. Data from fee-for-service private insurance claims in the USA were used. The 1-year total direct health care costs were found to be lower for patients initiating therapy on fluoxetine compared to patients initiating therapy on a TCA and lower for patients who initiated therapy on fluoxetine than for patients initiating therapy on sertraline. The authors conclude that the findings of the study suggest that total direct health care costs differ across initial antidepressant selection.

In conclusion, RCTs are essential to demonstrate efficacy of new drugs, but pharmacoepidemiological research makes it possible to get additional insights in effectiveness and safety of psychotropics in clinical practice.

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CHAPTER 2

Psychotropic drug use in psychiatric admission wards

- 2.1 Short-acting parenteral antipsychotics drive choice for classical versus atypical agents
- 2.2 Antipsychotics and seclusion in hospitalised patients: treatment pathways

CHAPTER 2.1

Short-acting parenteral antipsychotics drive choice for classical versus atypical agents

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ABSTRACT

The introduction of atypical antipsychotics has changed treatment options for psychotic disorders dramatically. There has been a large shift favouring the use of atypical antipsychotic agents, although their precise therapeutic value remains controversial. The objective of this study was to investigate the factors affecting the choice of antipsychotic agents (classical versus atypical) given first to newly hospitalised patients. A nested case control study was conducted in a cohort of 522 patients treated with an oral antipsychotic drug. Recipients of an atypical agent were considered as cases (27.8% of patients). Controls were all other cohort members. No statistically significant difference was found between patients suffering varying degrees of disease severity. Patients treated with classical oral antipsychotics had more often received short-acting parenteral antipsychotics earlier than patients treated with atypical antipsychotics (40.8% versus 15.2%) (adjusted odds ratio: 0.14; 95% confidence interval: 0.07-0.29). Availability of injectable forms seems to be a major factor in the choice of oral agents later prescribed for psychosis. Thus, future introductions of short-acting parenteral atypical formulations are likely to have a large impact on the choice of oral treatments prescribed for psychosis.

INTRODUCTION

Antipsychotic drugs are essential in the treatment of patients suffering from psychotic disorders, both in clinical and community settings [1]. Over 20 drugs with varying pharmacological properties are currently available for treatment of psychotic disorders. Classical or typical antipsychotic drugs, including haloperidol and pimozide, are widely used as first-line treatment for psychotic disorders, in acute as well as in chronic forms of the illness [2]. However, these substances have a relatively limited effect on negative symptoms associated with schizophrenia, i.e. lack of speech, lack of motivation, apathy and inability to express emotions [3]. Moreover, their use is associated with adverse effects, including extrapyramidal symptoms (EPS) often resulting in non-compliance or premature discontinuation [4, 5].

The introduction of atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine and ziprasidone) has changed treatment options for psychotic disorders dramatically. There has been a large shift favouring the use of these atypical antipsychotic agents [6], although their precise therapeutic value remains controversial [7-13]. Their effect on negative symptoms is not fully elucidated. Newer agents seem to be superior with regard to risk on EPS, but they have been associated with other side effects, such as weight gain [14]. Official therapeutic guidelines, including the one on the pharmacotherapy of psychotic disorders in the Netherlands [15], have not yet decided between classical or atypical antipsychotics as first-line treatment. For insight into prescribing patterns of these drugs in daily practice and factors that affect the choice between classical and atypical antipsychotics, an observational study within a well-defined group is needed.

The objective of our study was to investigate which class of antipsychotic drugs (classical versus atypical) is used preferentially in newly admitted psychiatric patients and the determinants affecting this choice.

METHODS

Setting and study population

Data were retrospectively collected from the acute psychiatric admission wards of three psychiatric hospitals, serving a catchment area of about 720,000 inhabitants in the centre of the Netherlands, during 1997-1999. Patients, aged between 18 and 60 years, who were admitted for a new hospitalisation of at least 3 days were included in the cohort. 'Newly hospitalised' was defined as having no previous admission to the psychiatric centre for any indication in the 2 years before the inclusion date. We reviewed data from 1995 for the 1997 admissions.

Design

In a retrospective cohort design, patients were followed from date of admission until discharge from the hospital. In the cohort of newly admitted patients treated with an oral antipsychotic drug, a nested case control study was conducted considering recipients of an atypical agent as cases. Controls were all other cohort members.

The drug use database and the clinical database were linked anonymously through record linkage methodology based on date of birth, gender and date of admission [16]. At admission, diagnoses were coded according to DSM-IV [17] criteria by the treating psychiatrists. Patients were rated on the Global Assessment of Functioning (GAF), with a low GAF score denoting more severe illness. The admission wards were classified as 'open' or 'closed'. Closed wards have limited access after admission and are reserved for more severely ill patients.

All medication was classified according to the ATC-classification system [18]. Antipsychotics (ATC-code N05A) were classified as classical or atypical. Lithium, levomepromazine and promethazine are not registered for psychotic disorders in the Netherlands and were, therefore, excluded. Clozapine, olanzapine, risperidone, sertindole and quetiapine were classified as atypical antipsychotics; other drugs with 4 digits ATC-code N05A were classified as classical antipsychotics. Drugs were also stratified according to their route of administration: oral or parenteral. We differentiated between parenteral short-

acting (e.g. haloperidol- and zuclopenthixol-acetate) and long-acting (depot) antipsychotics. We excluded 31 patients who either received both an oral classical and atypical antipsychotic on the day of admission or received only depot antipsychotics.

The Scientific Committee and the board of the Centre for Mental Health approved the study protocol with respect to privacy aspects.

Analysis

The overall utilisation patterns of oral antipsychotics over time were ascertained by calculating the prevalence of drug use on the second Wednesday of each quarter between 1997 and 1999. The incidence of new antipsychotic drug users was also calculated for each quarter. We calculated the relative incidence and prevalence for both classes by expressing the values as percentages of total antipsychotic drugs used.

Odds ratios were calculated for factors possibly associated with the choice between classical versus atypical antipsychotics (age, gender, all DSM-IV diagnoses, use of short-acting parenteral antipsychotic, GAF score and type of ward). Logistic regression was used to adjust for possible confounders (age group, gender, DSM-IV diagnoses, use of short-acting parenteral antipsychotic). Data were analysed using EGRET statistical software.

RESULTS

The characteristics of the cohort members are presented in Table 1. A total of 522 patients met the inclusion criteria. Most patients (60.9%) were younger than 40 years with a median age of 36 years. Psychotic disorders accounted for 50.2% of the diagnoses of the patients admitted. Other diagnoses included bipolar (16.3%), depressive (12.6%), and personality disorders (16.7%). The most frequently prescribed oral antipsychotic drugs were zuclopenthixol (33.7%), pimozide (13.4%) and haloperidol (12.6%). The proportion of atypical agents was 27.8%, consisting of clozapine (1.9%), olanzapine (14.8%) and risperidone (11.1%). While the total proportion of incident prescriptions of atypical antipsychotics increased only slightly from 27.2% to 35.1%, initial prescription of olanzapine increased over the years 1997 until 1999 from 7.8% to 19.6%.

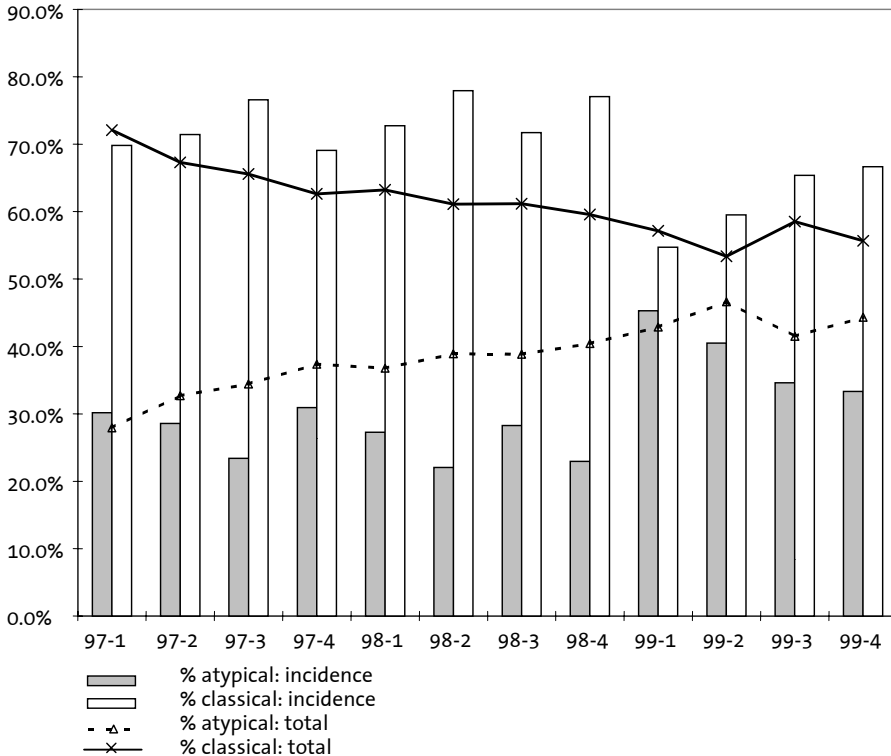
Table 1. Characteristics of 522 newly admitted patients using antipsychotics.

	n (%)
Age (years)	
<40	318 (60.9%)
≥40	204 (39.1%)
Median	36
Gender	
Male	273 (52.3%)
Female	249 (47.7%)
Any diagnosis (DSM-IV)*	
Schizophrenia and psychotic disorder	262 (50.2%)
Bipolar disorder	85 (16.3%)
Depressive disorder	66 (12.6%)
Other	23 (4.4%)
Unknown	65 (12.5%)

A third of patients was initially treated with a short-acting parenteral antipsychotic drug. A vast majority of this group (94%) was treated with zuclopenthixol-acetate, a parenteral formulation that acts for 2-3 days.

Figure 1 depicts the ratio between incident users of classical versus atypical oral antipsychotics in each 3-month period from January 1997 to December 1999. The proportion of users starting an atypical antipsychotic was stable at around 30%. In the same figure, the proportion of prevalent use of classical and atypical oral antipsychotics over time is depicted. The fraction of oral atypical antipsychotic use increased between 1997 and 1999 from 28.8% to 44.3% in relation to the total amount of oral antipsychotic use.

Figure 1. Relative incidence and prevalent use of oral classical and atypical antipsychotics 1997-1999.



In Table 2, possible determinants of type of first oral antipsychotic use are listed. We found that 154 (40.8%) out of 377 patients treated with classical oral antipsychotics were initially treated with short-acting parenteral formulations. This was 15.2% in the group treated with an oral atypical antipsychotic (adjusted odds ratio: 0.14; 95% confidence interval: 0.07-0.29). The use of atypical agents was significantly lower in patients with bipolar disorders (adjusted odds ratio: 0.30; 95% confidence interval: 0.11-0.80). No statistically significant difference was found between patients with varying severity of disease, indicated by GAF score and type of ward (open versus closed). GAF scores were missing in 180 (34.4%) patients. Analysis revealed that most missing GAF scores were from the 1997 admissions, in which 64.6% of GAF scores was missing, while in 1998 and 1999, 13.6% and 26.3% were missing, respectively.

Table 2. Factors associated with choice of first oral antipsychotic (N = 522). Crude odds ratios and adjusted odds ratios with 95% confidence interval (95% CI) of atypical antipsychotics compared to classical antipsychotics. Significant associations are printed in bold.

	Atypical antipsychotics (n = 145) (%)	Classical antipsychotic (n = 377) (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age				
<40	96 (66.2)	222 (58.9)	1.0 (reference)	1.0 (reference)
≥40	49 (33.8)	155 (41.1)	0.7 (0.5-1.1)	0.8 (0.4-1.4)
Gender				
Male	81 (55.9)	192 (50.9)	1.0 (reference)	1.0 (reference)
Female	64 (44.1)	185 (49.1)	0.8 (0.6-1.2)	0.74 (0.42-1.30)
Initial short-act. parent. antipsychotic				
	22 (15.2)	154 (40.8)	0.3 (0.2-0.4)	0.14 (0.1-0.3)
DSM-IV diagnosis *				
Psychotic disorder	78 (53.8)	184 (48.8)	1.2 (0.8-1.8)	1.19 (0.6-2.4)
Bipolar disorder	9 (6.2)	76 (20.2)	0.3 (0.1-0.5)	0.30 (0.1-0.8)
Depressive disorder	18 (12.4)	48 (12.7)	1.0 (0.5-1.7)	0.65 (0.3-1.7)
Personality disorder	21 (14.5)	66 (17.5)	0.8 (0.5-1.4)	0.48 (0.2-1.1)
Anxiety disorder	7 (4.8)	19 (5.0)	1.0 (0.4-2.3)	0.55 (0.2-1.9)
Other disorder	8 (5.5)	15 (4.0)	-	-
Unknown disorder	25 (17.2)	40 (10.6)	-	-
Global Assessment of Functioning (GAF)				
<35	33 (22.8)	99 (26.3)	1.0 (reference)	1.0 (reference)
35-55	43 (29.7)	127 (33.7)	1.0 (0.6-1.7)	1.06 (0.6-1.9)
≥ 55	15 (10.3)	25 (6.6)	1.8 (0.9-3.8)	1.78 (0.8-4.1)
Missing GAF	54 (37.2)	126 (33.4)	-	-
Type of ward				
Open ward	49 (33.8)	100 (26.5)	1.0 (reference)	1.0 (reference)
Closed ward	96 (66.2)	277 (73.5)	0.71 (0.5-1.1)	0.73 (0.4-1.4)

*Totals may exceed 100% because of multiple diagnoses.

DISCUSSION

We found that a stable proportion of patients was started on atypical oral antipsychotics during the study period. About one third of all new antipsychotic users received an atypical agent. We noted an increase in the use of atypical antipsychotics which means that patients were either using atypical agents for longer periods of time, or were more often switched from classical to atypical agents than vice versa.

Patients with psychotic illnesses may have delusions or hallucinations that may lead them to be aggressive or violent to themselves or others. Medication that is used in this context requires the property of a rapid onset of effect (tranquillisation or at least initial sedation in order to control aggressive or disorganised behaviour) [19]. An antipsychotic effect is also needed, but cannot be expected within one or two weeks. In this context, it is an unexpected finding that our two markers of disease severity, GAF scores and type of ward (open or closed) of patients receiving oral atypical agents did not differ from those treated with oral classical agents, suggesting that severity of disease is not a determinant for the choice of drug used between these patient groups.

This study showed that availability of injectable forms seems to affect the selection of the follow-up oral antipsychotic agent. Seven times as many patients treated with oral classical agents compared to oral atypical agents were initially treated with short-acting parenteral agents. The choice for one of the available injectable forms with immediate action, frequently done in a situation when rapid response to a psychotic crisis is needed, affects follow-up treatment scenarios, assuming the administration of an antipsychotic drug results in a positive effect (e.g. control of aggression) on the acute status of the patient. As a result, the physician will often choose to continue the same type of medication in an oral formulation. Choice of the follow-up oral medication seems to express the satisfaction of the effect of the short-acting parenteral antipsychotic on the non-psychotic symptoms.

At the time of this study, Dutch guidelines for prescribing antipsychotics in schizophrenic psychosis [15] have not yet decided between classical and atypical agents for first-line treatment. In our three study hospitals, no financial

or administrative barriers were made to prevent physicians from prescribing new and expensive atypical antipsychotics. In literature, the debate on choice for first-line treatment of psychosis is also still ongoing. In a recently published meta-analysis studying 52 randomised-controlled trials of atypical antipsychotic drugs in the treatment of schizophrenia, Geddes et al [8] concluded that atypical agents are not better tolerated than typical agents. They recommended that classical antipsychotics should be the first-line treatment for schizophrenia. This same review has, however, been extensively criticised, arguing that for the majority of patients atypical antipsychotics should be used as first-line drugs [20-26].

We found a large difference between the initial use of classical and atypical antipsychotics in bipolar disorders although the Dutch guidelines for pharmacotherapy of these disorders are inconclusive [27].

There are some limitations to our study. Although one could argue that only data on admitted patients were available, we were, however, interested in the more severely ill patients who were admitted to a psychiatric hospital. Another limitation is the possibility that our selection of newly admitted patients may contain some patients previously admitted in another region before moving to the catchment area of our hospital. Since patients in the Netherlands are preferably transferred to their home region, this would only apply to a minority of the included patients. Although we collected data from only three hospitals, their catchment area is very large and admission in most cases would lead to admission to one of the investigated hospitals.

More than 30% of GAF scores were noted to be missing, with the most missing scores connected to the 1997 admissions when it was not yet common practice to record GAF scores into the hospital database. More attention was given to this subject in 1998 and 1999. We found that patients with available GAF scores did not differ in gender, age and only slightly in diagnostic categories when compared to patients with missing GAF scores. It is, therefore, likely that our data are representative for the total population of patients. The other marker of disease severity (type of ward) also showed the same sort of result.

Parenteral formulations of only classical antipsychotic agents are presently available. Our study reveals that initial use of short-acting parenteral antipsychotics is (also after adjusting for possible confounding factors) a major determinant for the choice of the follow-up oral treatment. We anticipate that upcoming introductions of short-acting parenteral formulations of atypical agents are likely to have a large impact on the follow-up oral antipsychotic treatment. Because of much higher pricing of atypical antipsychotics, a shift in favour of the atypical antipsychotics would also be expected to have a major effect on hospital budgets. Another investigation of the determinants affecting the selection of oral antipsychotics may be warranted after introduction of a short-acting parenteral formulation of an atypical agent.

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CHAPTER 2.2

Antipsychotics and seclusion in hospitalised patients: treatment pathways

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ABSTRACT

Seclusion is one of the strategies to cope with disruptive and violent behaviour in psychiatric patients. Situational factors including psychotropics in relation to seclusion have hardly been studied. We wanted to identify possible determinants of seclusion and gain insight into the temporal relationship between seclusion and the use of antipsychotics in newly admitted patients. Data were retrospectively collected for the years 1997-1999 from a consecutive sample of 996 patients from adult psychiatric admission wards. In a nested case-control analysis, secluded and non-secluded patients were compared. In another analysis, patients were followed from admission to a week after the first seclusion. We found that young age, low GAF score, involuntary hospitalisation and bipolar disorder (manic episode) were significantly associated with seclusion, applicable to 28.6% of the patients. Antipsychotic treatment early in the hospitalisation was associated with a delay of seclusion and, although not statistically significant, with a lower risk of seclusion. In a substantial part of the population, antipsychotic treatment was initiated during or shortly after seclusion. In conclusion, (forced) pharmacological treatment appears inevitable for a substantial proportion of secluded psychotic patients. It is likely that earlier use of antipsychotics may prevent patients from being secluded.

INTRODUCTION

In psychiatric inpatient care, seclusion is one of the strategies to cope with disruptive and violent behaviour [1-3]. Compared to the relatively large number of studies on the characteristics of secluded patients, situational factors in relation to seclusion have hardly been studied [3, 4]. Remarkably, this is also the case for the relationship between psychotropics and the application of seclusion. In the Netherlands, involuntary hospitalisation does not mean that patients can be treated pharmacologically against their will. Special treatment methods, such as seclusion and involuntary medication, may only be applied in involuntarily hospitalised patients, in case of serious danger to the patient or others, with the exclusion of emergencies.

In the current study of hospitalised patients on acute admission wards, we sought to identify determinants of seclusion and to investigate the temporal relationship between seclusion and the use of antipsychotics.

MATERIALS AND METHODS

Patients and data collection

Data were retrospectively collected from a consecutive sample of 996 patients aged 16 years or older concerning their first complete hospitalisation of four days or longer in one of the participating admission wards during 1997-1999. The admission wards with a total of 250 beds are part of three general psychiatric hospitals in the centre of the Netherlands, recently merged to one large institute for mental health care with a total catchment area of 720,000 persons. Patient characteristics, data on the use of seclusion and antipsychotics were extracted from the patient database and a linked automated database of the pharmacy. The Scientific Committee and the board of the Centre for Mental Health approved the study protocol with respect to privacy aspects.

Databases

The hospital patient database contains demographic data, diagnoses, admission and discharge dates, and data on seclusion. In the automated pharmacy database, every initiation and subsequent change in the prescription of medication is recorded. Both databases contain information on date of birth,

gender and date of admission, allowing the two databases to be linked anonymously. In a validation study, the linkage success of 150 randomly selected patients was greater than 95%.

Psychiatric diagnosis and antipsychotic treatment

At admission, (multiple) psychiatric diagnoses were established by the psychiatrists on the wards according to DSM-IV criteria [5] (schizophrenia and other psychotic disorders, substance-induced psychotic disorders, depressive disorders, anxiety disorders, bipolar disorders, personality disorders). Patients were rated on the Global Assessment of Functioning (GAF), with a low GAF score denoting more severe illness.

Medication was coded according to the WHO Anatomical Therapeutic Chemical (ATC) coding system. Data on antipsychotics (ATC-code N05A) were collected, excluding droperidol, levomepromazine and promethazine that are mainly prescribed for sedation in the Netherlands and lithium that is mainly used as a mood stabiliser.

Data Analysis

In the nested case-control analysis, secluded patients were compared to non-secluded patients. Odds ratios were calculated to evaluate the possible effects on seclusion of age, gender, (in)voluntary hospitalisation, psychiatric diagnosis and GAF score. Unconditional logistic regression analysis was used. All seclusions were included in this analysis.

In the follow-up analysis, patients were followed from admission to a week after the first seclusion, or from admission to a week after an index date at a proportional point in time during hospitalisation. Patients, secluded immediately at the time of admission, were excluded because no data on medication use prior to seclusion were available for these patients. We analysed time from the admission date to the first seclusion comparing patients with and without using antipsychotics in the first week of hospitalisation. Hazard ratios were calculated using Cox proportional hazards survival analysis. Relative risks were calculated for patients using antipsychotics in the first week of hospitalisation prior to seclusion compared

to non-users. Relative risks were calculated for patients not using antipsychotics prior to seclusion and starting antipsychotics during, or shortly, after seclusion compared to non-secluded patients using antipsychotics. All analyses were performed with SPSS Package and EGRET.

RESULTS

Basic characteristics

The mean age of the population of 996 patients was 38.0 years (median: 37.0 years; range: 16-84 years). The number of male patients, 507 (50.9%), was almost equivalent to the number of female patients. The mean duration of hospitalisation was 57.2 days (median: 24.0 days; range: 4-711 days). Psychotic disorders were most prevalent: 398 of the 996 patients (40.0%). Little more over a quarter of the patients (i.e. 285 of 996 patients or 28.6%) had been secluded at least once during their hospitalisation.

Patient-related factors associated with seclusion

In Table 1, possible factors associated with seclusion are listed. Young age was significantly associated with seclusion as was a lower GAF score between 35-55 and below 35, indicating major impairment in functioning. Involuntarily hospitalised patients were more likely to be secluded than voluntarily hospitalised patients with an odds ratio of 4.9 (95% confidence interval: 3.5-6.9). Of the psychiatric diagnoses, only bipolar disorder (manic episode) was significantly associated with seclusion.

Time to seclusion

The mean time from admission to seclusion among patients with psychotic disorders who used antipsychotics during the first week was 21.6 days (median: 7.0 days; range 1 to 235 days). In patients not using antipsychotics this was 15.2 days (median: 2.5 days; range 1 to 213 days). Figure 1 shows a Kaplan-Meier plot during the first month of hospitalisation in this population. We found that antipsychotic use was significantly associated with a delay of seclusion with an adjusted (gender, age, GAF score) hazard ratio of 0.6 (95% confidence interval: 0.3-1.0).

Table 1. Factors associated with seclusion in hospitalised patients (N = 996). Crude odds ratios and adjusted* odds ratios with 95% confidence interval (95% CI) of secluded patients compared to non-secluded patients. Significant associations are printed in bold.

	Secluded (n = 285) (%)	Non-secluded (n = 711) (%)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Gender				
Female	119 (41.8)	370 (52.0)	1.0 (reference)	1.0 (reference)
Male	166 (58.2)	341 (48.0)	1.5 (1.1-2.0)	1.4 (1.0-1.8)
Age				
16-30	103 (36.1)	170 (23.9)	2.7 (1.7-4.1)	2.2 (1.4-3.5)
30-40	89 (31.2)	202 (28.4)	1.9 (1.2-3.0)	1.6 (1.0-2.6)
40-50	59 (20.7)	190 (26.7)	1.4 (0.8-2.2)	1.0 (0.6-1.7)
>50	34 (11.9)	149 (21.0)	1.0 (reference)	1.0 (reference)
Global Assessment of Functioning (GAF)**				
<35	79 (39.8)	109 (26.1)	2.3 (1.3-4.0)	3.4 (1.8-6.3)
35-55	96 (49.0)	240 (57.4)	1.3 (0.7-2.1)	2.0 (1.1-3.7)
>=55	22 (11.2)	69 (16.5)	1.0 (reference)	1.0 (reference)
Type of hospitalisation				
Voluntary	164 (57.5)	620 (87.2)	1.0 (reference)	1.0 (reference)
Involuntary	121 (42.5)	91 (12.8)	5.0 (3.6-6.9)	4.9 (3.5-6.9)
Psychiatric diagnosis (DSM-IV)†, ††				
Psychotic disorder	127 (46.7)	271 (39.8)	1.3 (1.0-1.7)	1.2 (0.9-1.7)
Depressive disorder	34 (12.5)	123 (18.1)	0.6 (0.4-1.0)	0.7 (0.4-1.1)
Anxiety disorder	15 (5.5)	32 (4.7)	1.2 (0.6-2.2)	1.5 (0.8-3.1)
Bip. Disorder-manic	37 (13.6)	58 (8.5)	1.7 (1.1-2.6)	1.8 (1.1-3.1)
Personality disorder	60 (22.1)	150 (22.1)	1.0 (0.7-1.4)	1.2 (0.8-1.8)

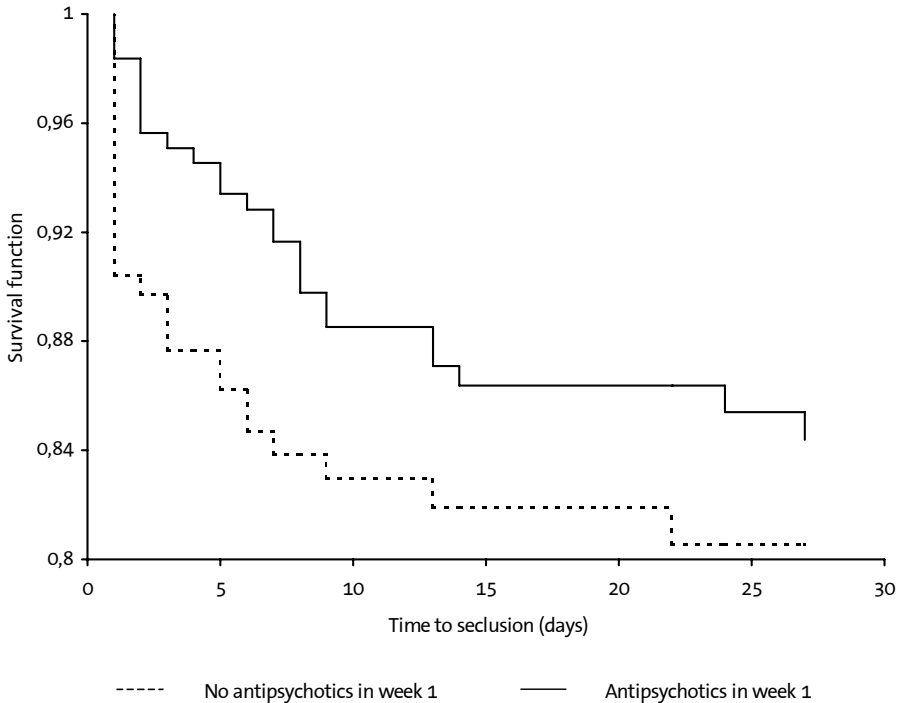
*adjusted for gender, age, type of hospitalisation, psychiatric diagnosis.

**n = 615 due to missing values.

†n = 952 due to missing values.

††according to DSM IV, multiple diagnoses could be established.

Figure 1. A Kaplan-Meier plot of the time from the first day of hospitalisation to seclusion, comparing patients using and those not using antipsychotics.

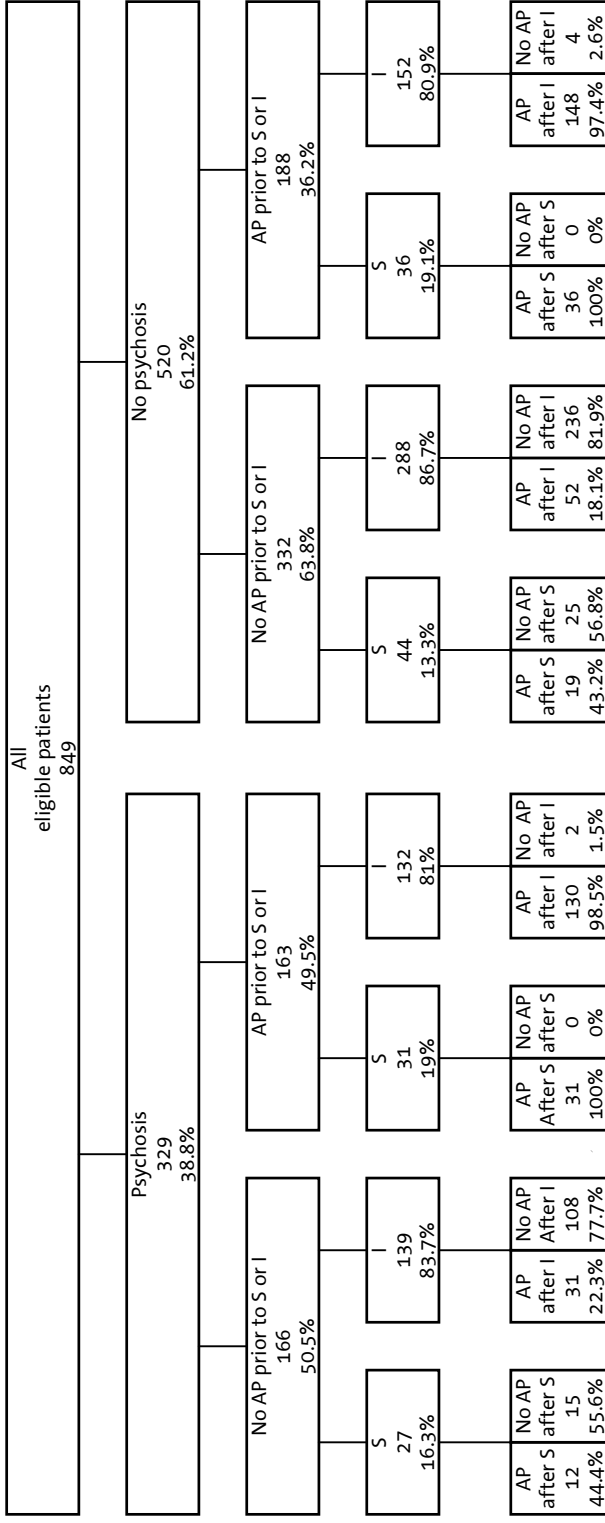


The temporal association of antipsychotics with seclusion

We found that among patients with psychotic disorders, 15.3% who used antipsychotics prior to seclusion during the first week of hospitalisation was secluded compared to 20.5% of those not using antipsychotics during the first week. This corresponds with a relative risk of 0.7 (95% confidence interval: 0.5-1.2).

Figure 2 shows that, in non-psychotic patients, 19 out of 44 (43.2%) started using antipsychotics during or directly after seclusion compared to 52 out of 288 (18.1%) of non-secluded patients directly after the index date, corresponding with a relative risk of 2.4 (95% confidence interval: 1.6-3.6). When looking specifically at patients with psychotic disorders, we also found that seclusion often preceded the prescription of antipsychotics with a relative risk of 2.0 (95% confidence interval: 1.2-3.4).

Figure 2. The temporary relationship between antipsychotics (AP) and seclusion (S) or an indexdate (I). Patients secluded immediately at the time of admission (n = 147) were excluded.



DISCUSSION

Prevalence of seclusion

The overall prevalence of seclusion found in the current study was high compared to other European countries [6, 7]; more than a quarter (i.e. 28.6%) of hospitalised psychiatric patients was secluded at least once during hospitalisation. This may be related to the Dutch legal situation where involuntary hospitalisation does not mean that the patient has to accept the proposed treatment.

Patient-related factors associated with seclusion

Young age, low GAF score and involuntary hospitalisation were significantly associated with seclusion. It is likely that agitation and aggression are particularly serious problems in the group of severely ill involuntarily hospitalised young patients for whom seclusion is needed. We found a significant association between bipolar disorder (manic episode) and seclusion, but rather unexpectedly, no clear association between psychotic disorder and seclusion. This is in contrast with other studies in which it was found that patients with psychotic disorders showed an increased seclusion rate [1, 8, 9].

Treatment pathways

We found that a delay of seclusion was significantly associated with the use of antipsychotics. Patients with psychotic disorders who accepted antipsychotics during the first week of hospitalisation were at a lower risk of seclusion than patients who did not use these agents, although this difference was not statistically significant. Our findings are in accordance with the findings of Hoge et al [10] and Kasper et al [11] who found that patients with psychotic disorders who refused treatment were significantly more likely to require seclusion. Our findings are also in line with the studies of Chiles et al [12] and Chengappa et al [13] who found that treatment with either clozapine or risperidone was associated with a significant reduction in the use of seclusion. Apparently, in patients with psychotic disorders, not accepting antipsychotics is associated with aggression or violence for which seclusion is needed. Subsequently, in a substantial proportion of patients, antipsychotic treatment was initiated only during, or directly, after seclusion.

Limitations of the study

A limitation of our study is that 38.3% of the GAF scores at admission were missing in our database. However, patients with available GAF scores did not differ in gender, age and duration of hospitalisation and only slightly in diagnostic categories when compared to patients with missing GAF scores. It is therefore likely that our data are representative for the total population of patients.

Because of the observational study design, it is possible that confounding factors influenced the observed associations. Therefore, causal associations must be carefully interpreted. It is possible that patients not using anti-psychotics prior to seclusion (probably due to non-compliance) were more severely ill and therefore more likely to be secluded than patients who used these agents [10, 11]. However, after adjusting for GAF score, we still found a significant hazard ratio.

Implications of the study

To our knowledge this is the first time that the temporal relationship between antipsychotics and seclusion has been studied. There is an ongoing debate on the application of seclusion in relation to the use of involuntary medication in the Netherlands. According to the Dutch law, involuntary hospitalisation does not automatically mean that the patient can be involuntarily treated with psychotropics (this is in contrast with, for example, the UK). The choice between coercive measures is left to the treating physician. It should be primarily focused on the purpose of the measure (i.e. warding off serious danger) and it should infringe as little as possible on the rights of the patient. The results of our study suggest that seclusion is generally considered as less infringing than involuntary medication, but our results also suggest that in the end (forced) pharmacological treatment remain inevitable for a substantial proportion of secluded psychotic patients.

Our findings underline the question as to what is preferable for patients who are aggressive or violent during their stay on an admission ward: seclusion or treatment with antipsychotics? Antipsychotics are considered essential in both international and Dutch guidelines for the treatment of patients with psychotic disorders [14, 15]. Moreover, antipsychotics are also indicated (and registered

in the Netherlands) for the treatment of severe agitation, including aggression. Seclusion may have serious physical and psychological adverse effects for the patient [9, 16]. In addition, during the application of seclusion, staff members run the risk of getting injured [17, 18]. On the other hand, involuntary medication may also have considerable (psychological) adverse effects, which, however, have not been empirically substantiated [19]. No studies on the effectiveness of seclusion are available [3].

In conclusion, we found that the use of antipsychotics was associated with a delay of seclusion. Apparently antipsychotics do lead to a reduction of agitation and aggression both in psychotic and non-psychotic patients. Thus, it is likely that their use also leads to a lower risk of seclusion. In a substantial proportion of our patients, antipsychotic treatment was initiated shortly after starting seclusion. It is likely that in the end (forced) pharmacological treatment is inevitable for a substantial proportion of secluded psychotic patients. Probably, earlier (involuntary) use of antipsychotics might have prevented patients from being secluded. Therefore, we recommend the reconsideration of earlier (involuntary) application of antipsychotics in agitated and aggressive (psychotic) patients. Moreover, we recommend more detailed investigations into the association between antipsychotics and seclusion.

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CHAPTER 3

Psychotropic drug use in a general intensive care unit

- 3.1 Determinants of psychotropic drug usage in a general intensive care unit
- 3.2 Correlated measures in longitudinal analysis of daily drug use patterns in a general intensive care unit

CHAPTER 3.1

Determinants of psychotropic drug usage in a general intensive care unit

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ABSTRACT

During a 3-months period, determinants of psychotropic drug utilisation (gender, age, length of stay, reason for admission, disease severity) and data on psychotropic consumption (type of medication -antidepressants, benzodiazepines and antipsychotics-, dosage and length of treatment) were retrospectively collected in a general intensive care unit of a Dutch university hospital. Daily exposure to psychotropics was standardised in number of Defined Daily Doses (DDD). Benzodiazepines were used by 35.8% of all patients (137) during their stay in the ICU whereas 17.5% of all patients used a neuroleptic agent. Antidepressants were hardly prescribed. High doses of benzodiazepines (9.9 DDDs) and low doses of antipsychotics (0.5 DDDs) were prescribed which probably reflect the outlandish nature of this critically ill group of patients with the reference group for DDDs. Clear patterns of determinants of psychotropic drug use in ICU patients were found and both benzodiazepines, antipsychotics and combined use of these agents could be associated the determinants assessed. The time patterns we found in terms of length of stay give clues for further investigations in order to rationalise psychotropic drug use in the management of severely ill and complex patients.

INTRODUCTION

Derangement of emotion, cognition and behaviour are frequently encountered in intensive care settings [1]. The administration of psychotropic drugs is one of the mainstay strategies to cope with these problems. The use of psychotropic drugs in our Intensive Care Units (ICUs) was shown to be among the highest in non-psychiatric departments in this hospital based on a 30% of the total consumption of neuroleptic agents [2]. Elsewhere, the highest use of parenteral benzodiazepines was seen in the ICU [3].

Little is known about the determinants of frequent administration of psychotropic drugs in critical care settings. Indications for sedation during critical illness commonly centre on patient comfort and acceptance of invasive treatment, supplemented by analgesics when called for. Drug dosing for sedation and psychic stability are ideally based on regularly assessed individual needs and verified according to sedation scores [4]. The often stormy course of critical illness often complicates such assessment. Moreover, fine tuning drug dosing of psychotropics in ICU patients is complicated by highly variable patterns of drug metabolism and elimination [5].

In order to gain insight in the heavy use of psychotropic drugs we sought to identify the determinants of prescription in our intensive care by a retrospective analysis based on daily drug dosages per bed-day.

MATERIALS AND METHODS

Population and data

Data were retrospectively collected over the first three months of 1995 from a consecutive sample of 137 patients of 18 years or over admitted to two general ICU's (17 beds in total). In these units surgical and non-surgical critically ill adult patients are admitted. Patient data (gender, age, length of stay, reason for admission, disease severity) and data on psychotropic consumption (type of medication -antidepressants, benzodiazepines or antipsychotics, dosage and length of treatment) were extracted from the medical records by means of a standardised data collection form. The study protocol has been approved by the Ethics Committee of the University Hospital Nijmegen.

The Acute Physiologic and Chronic Health Evaluation (APACHE)-II classification system [6] was used to classify patients according to severity of disease on admission. This system utilises a score (range 0-71) based on worst values over 24 hours of 12 routine physiologic measurements, age and previous health status to provide a standardised measure of severity of disease. The height of the score is correlated with the subsequent risk of hospital death [6]. We arbitrarily stratified patients according to APACHE-II scores into three groups of low (0-10), middle (11-20) and high (>21) severity of disease.

Medication was coded according to the WHO Anatomical Therapeutic Chemical (ATC) coding system. Daily exposure to psychotropics was standardised in number of Defined Daily Doses (DDD), a standardised technical unit of measurement defined as the average dose per day for a drug used for its main indication in adults [7]. Medication termed 'as needed' was not included in the analysis. If the dose changed during the day, the highest dose was noted.

Analysis

In order to cope with varying lengths of stay in the ICU 'bed-days' were taken as unit of analysis, excluding non 24 hour admission days, effectively omitting the day of admission and discharge. The odds of psychotropic drug use (benzodiazepines, antipsychotics or both) per day were calculated comparing exposed days with non-exposed days. In this way a single patient could contribute to both exposed and unexposed days. Adjustment for possible confounding was performed by an unconditional logistic regression analysis. Data were analysed using EGRET (Epidemiological GRaphics Estimation and Testing package) [8] and SPSS (Statistical Package for the Social Sciences) [9].

Table 1. Psychotropic drug use in an ICU, number of patients, number of days one or more drugs were used, average number of days a drug was used and average daily dose.

	Number of patients (n = 137) n(%)	Number of days (n = 734) n(%)	Average number of days used	Average daily dose (DDDs/day)
Any psychotropic	58 (42.3)	347 (47.3)	6.0	5.9
Benzodiazepines	49 (35.8)	255 (34.7)	5.2	9.9
Midazolam	37 (27.0)	133 (18.1)	3.6	13.5
Oxazepam	14 (10.2)	32 (4.4)	2.3	0.2
Diazepam	10 (7.3)	13 (1.8)	1.3	0.9
Clorazapate	6 (4.4)	79 (10.8)	13.2	9.1
Clonazepam	2 (1.5)	5 (0.7)	2.5	2.1
Antipsychotics	24 (17.5)	196 (26.7)	8.2	0.5
Levomepromazine	23 (16.8)	172 (23.4)	7.5	0.4
Haloperidol	5 (3.6)	12 (1.6)	2.4	0.7
Alimemazine	2 (1.5)	18 (2.5)	9.0	0.5
Chlorpromazine	1 (0.7)	2 (0.3)	2.0	0.3
Trifluoperazine	1 (0.7)	7 (1.0)	7.0	2.0
Antidepressants				
Amityriptiline	1 (0.7)	1 (0.1)	1.0	0.3

RESULTS

The 137 patients accounted for 734 bed-days in the ICU. The mean age of the patients was 54.1 years ranging from 18 to 83 years. Male patients (59.9%) outnumbered female patients. The mean APACHE score was 13.6 ranging from 1 to 41. One out of two patients were classified in the medium APACHE group (score 11-20). We stratified patients according to reason for admission into surgical ICU admissions and other reasons, mostly severe internal diseases. Surgical patients had an average stay of 2.7 days in the ICU while non-surgical patients showed an average stay of 8.0 days.

A total of 58 patients (42.3%) used one or more psychotropic agents during their stay in the ICU. These patients had an average stay of 10.7 days and a median stay of 2.2 days ranging from 1 to 82 days. In contrast, the average ICU stay for patients without psychotropic drug use was 1.5 days, median 1.0 days, ranging from 0 to 11 days. Table 1 presents data on the use of individual psychotropic agents. Benzodiazepines were used by 35.8% of all patients for an average of 5.2 days. Midazolam was the most commonly prescribed benzodiazepine, used by 27.0% of all patients and 75.5% of all benzodiazepine users. Antipsychotics were prescribed to 24 patients (17.5%), with levomepromazine as the most commonly prescribed neuroleptic, used by 16.8% of all patients and 96% of all neuroleptic users. Benzodiazepines were prescribed in high dosages; an average of 9.9 DDDs per day was used by patients on benzodiazepines. Especially midazolam was prescribed in very high dosages; an average of 13.5 DDDs, equivalent to 202.5 mg, per day. Antipsychotics on the other hand were prescribed in low dosages; an average use of 0.5 DDDs per day. Amitriptyline was the only antidepressant prescribed and it was used for a short period of one day in a low dosage of 0.3 DDD.

In Table 2, determinants of psychotropic drug use in ICU patients are listed, further compared according to adjusted odds ratios in Table 3. Benzodiazepines only were given significantly more to males, the patients aged 45-64 and to the middle (11-20) APACHE score group. Length of ICU stay and reason for admission were not significantly different for days of benzodiazepine use compared to days with no psychotropic use. Use of antipsychotics was significantly associated with males and here also, age 45-64 was significantly associated with an increased use of psychotropics as well as to the middle APACHE score group and a longer duration of stay. Admission to the ICU with a reason other than surgical was seen significantly more often in antipsychotic users compared to none-users. Combined use of benzodiazepines and antipsychotics was significantly more often seen in female patients and in age groups 18-44 and 65 years or over. There was also a strong association with higher APACHE scores and longer duration of stay in the ICU. Again, admission to the ICU with a reason other than surgical was associated with combined use of benzodiazepines and antipsychotics.

Table 2. Number of days of psychotropic use in ICU patients calculated for different gender, age, APACHE-II scores, length of stay and reasons for admission.

	None	Benzodiazepine only	Antipsychotic only	Benzodiazepine and antipsychotic
Total	387 (100%)	151 (100%)	92 (100%)	104 (100%)
Gender				
Female	205 (53.0)	52 (34.4%)*	15 (16.3%)*	82 (78.8%)*
Male	182 (47.0%)	99 (65.6%)*	77 (83.7%)*	22 (21.2%)*
Age				
18-44	73 (18.9%)	29 (19.2%)*	8 (8.7%)*	29 (27.9%)*
45-64	99 (25.6%)	64 (42.4%)*	39 (42.4%)*	7 (6.7%)*
>65	215 (55.6%)	58 (38.4%)*	45 (48.9%)*	68 (65.4%)*
Apache-II score				
0-10	60 (15.5%)	8 (5.3%)*	6 (6.5%)*	3 (2.9%)*
11-20	212 (54.8%)	104 (68.9%)*	63 (68.5%)*	54 (51.9%)*
>21	115 (29.7%)	39 (25.8%)*	23 (25.0%)*	47 (45.2%)*
Length of stay				
0-6	213 (55.0%)	85 (56.3%)	34 (37.0%)*	29 (27.9%)*
7-13	69 (17.8%)	22 (14.6%)	20 (21.7%)*	15 (14.4%)*
14-20	23 (5.9%)	10 (6.6%)	15 (16.3%)*	13 (12.5%)*
21-27	15 (3.9%)	4 (2.6%)	6 (6.5%)*	14 (13.5%)*
>28	67 (17.3%)	30 (19.9%)	17 (18.5%)*	33 (31.7%)*
Reason for admission				
Surgical	126 (32.6%)	45 (29.8%)	6 (6.5%)*	6 (5.8%)*
Non-surgical	261 (67.4%)	106 (70.2%)	86 (93.5%)*	98 (94.2%)*

*p-value<0.05

In order to adjust for possible confounding, we performed an unconditional logistic regression analysis including sex, age, APACHE score, number of days in the ICU and reason for admission in the logistic model (Table 3). Males were found to be exposed more bed-days to benzodiazepines whereas patients aged over 65 were less likely to use these agents. Moreover, high APACHE scores were significantly associated with increased use of benzodiazepines. There was no association found for benzodiazepine use with length of stay and reason for

admission. Antipsychotic use was found significantly more in males. Week 2 and 3 of stay at the ICU were strongly associated with a high use of antipsychotics as well as admission to the ICU for non-surgical reasons. Combined use of benzodiazepines and antipsychotics was especially seen in the lowest age groups as well as in patients with a higher APACHE score. Risk on combined use of benzodiazepines and antipsychotics increased with longer stay in the ICU with the highest risk in week 4. Again, admission for non-surgical reasons was associated with a higher combined use.

Table 3. Patient parameters associated with psychotropic drug use. Adjusted odds ratios with 95% confidence interval (95% CI) are compared in days of psychotropic use compared to days with no psychotropic drug use. Significant associations are printed in bold.

	Benzodiazepines Only (95% CI)	Antipsychotics only (95% CI)	Benzodiazepines and antipsychotics (95% CI)
Gender			
Female	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male	1.9 (1.2-3.1)	10.7 (4.9-23.2)	0.7 (0.3-1.4)
Age			
18-44	1.0 (reference)	1.0 (reference)	1.0 (reference)
45-64	0.8 (0.4-1.5)	0.8 (0.3-2.5)	0.1 (0.0-0.2)
>65	0.4 (0.2-0.8)	1.2 (0.4-3.3)	0.2 (0.1-0.5)
Apache-II score			
0-10	1.0 (reference)	1.0 (reference)	1.0 (reference)
11-20	4.7 (2.0-11.4)	1.5 (0.5-5.0)	11.5 (3.1-42.4)
>21	4.3 (1.7-10.9)	1.0 (0.3-3.6)	8.9 (2.3-35.0)
Length of stay			
0-6	1.0 (reference)	1.0 (reference)	1.0 (reference)
7-13	0.7 (0.4-1.3)	2.1 (1.0-4.3)	1.0 (0.5-2.1)
14-20	0.9 (0.4-2.0)	6.2 (2.4-16.2)	3.2 (1.3-8.1)
21-27	0.5 (0.2-1.6)	1.6 (0.5-5.4)	5.2 (2.0-13.4)
>28	0.9 (0.5-1.6)	1.6 (0.7-3.5)	2.2 (1.1-4.5)
Reason for admission			
Surgical	1.0 (reference)	1.0 (reference)	1.0 (reference)
Non-surgical	1.5 (0.9-2.6)	19.5 (7.1-53.9)	8.9 (3.2-24.7)

DISCUSSION

In this hospital's ICU's patterns of psychotropic drug use were distinguished against a background of fairly heavy use of benzodiazepines and a considerable use of neuroleptics. The high use of midazolam is in agreement with results of other studies [10-13]. Our findings of the use of benzodiazepines, prescribed to 35.8% of all patients and antipsychotics, prescribed to 17.5%, differ from currently available information on the use of psychotropic agents in critically ill patients. An increase in the use of benzodiazepines in a surgical ICU from 26% to 57% was prescribed between two periods in 1986-1987 and 1989-90, whereas the use of antipsychotics, specifically haloperidol, remained constant about 10% [13]. In another study benzodiazepines were prescribed in 43% of the patients in a surgical ICU [10]. The antipsychotic haloperidol was prescribed in 8.1% and droperidol in 0.4%. In a recent multi-center study drug administration data were collected for five days in 74 ICUs [14]. Of 1222 patients about 55% used benzodiazepines; neuroleptics were administered in circa 7%. It is likely that the patterns of psychotropic drug use differ amongst ICU's, based on differences in patient populations and local drug preferences. However our benzodiazepine use compared to these studies was low and neuroleptic use high. This could also be explained by the fact that in our study the phenothiazine levomepromazine was found to be used whereas in other studies benzodiazepines were used. This is interesting because phenothiazines may be used to potentiate the analgesic and sedative effects of analgetics but with the exception of anti-emetic effects they offer no substantial advantage over the more commonly used benzodiazepine-narcotic combination [15]. No comparison was made in our study to assess pain treatment.

Our data showed a very low antidepressant use. This probably represents the difficulty of making the diagnosis in this clinical setting [16], although depression is thought to occur with high frequency in the ICU patient population [17, 18].

This study revealed that high -in terms of DDDs- doses of benzodiazepines and low doses of antipsychotics were prescribed. These observations of unusual DDDs probably reflect the outlandish nature of this critically ill group of patients with the reference group for DDDs. The DDD as a unit of measurement

was primarily developed for ambulatory care settings, where much lower dosages of benzodiazepines and higher dosages of antipsychotics are customary. In the absence of widely accepted ICU sedation goals and means the introduction of the DDD as unit of analysis here may be seen as inappropriate. However, it helps to focus on a need to arrive at such standards. Reaching consensus will be a challenge in view of yet better defined and widely accepted assessment scores and the highly variable pharmacokinetics in ICU patients.

Our finding that patients were exposed to relatively small amounts of antipsychotics is in agreement with the results of Zitman et al. They found by interviewing senior consultants of the non-psychiatric departments that standard doses prescribed were well below the DDD [2]. Because the DDD was not used as a unit of comparison in other studies on the psychotropic use in ICUs it is not possible to compare our data to those of other studies.

In this study we found that benzodiazepine prescriptions are not as strongly associated with patient characteristics as is the use of antipsychotics only or combined with benzodiazepines. It is likely that benzodiazepines are primarily prescribed to attain a basic level of sedation. It is not known why there is a strong association between male sex and antipsychotic drug prescription. Physicians are probably more likely to prescribe a combination of benzodiazepines and antipsychotics because young patients have shorter elimination times for many agents compared to geriatric patients. However, this is not true for the frequently prescribed short half-life benzodiazepines such as midazolam which may not be an increased risk for the elderly [1]. High risk on the use of antipsychotics only or combined with benzodiazepines can be explained by the fact that a long stay in the ICU, high APACHE scores and an admission for non surgical reasons probably indicates severely ill patients who are likely to suffer from a delirium. Although no ideal sedative exists for this disorder haloperidol has been most often recommended for agitated, restless and frightened patients [1,19]. Some authors used this agent combined with a benzodiazepine when repeated doses of haloperidol failed to give a therapeutic response [1]. This combination may produce fewer extrapyramidal side effects [1]. An other explanation for the association of a long stay in the ICU with mainly combined use of benzodiazepines and antipsychotics is that the use of

these drugs prolongs stay in the ICU because of excessive sedation with cognitive impairment. In case of the first explanation it is conceivable that these drugs are under-utilised whereas in case of the second explanation these drugs are probably over-utilised. Because diagnostic data were not collected in this study, it was not clear whether the use of these drugs was appropriate or inappropriate.

The utilisation data of this study imply that side effects of benzodiazepines and antipsychotics must occur fairly regularly in the ICU. This stresses the need to search for these effects, even while they may be difficult to discern from other symptoms in obtunded, critically ill patients [2].

In conclusion, we found clear patterns of determinants of psychotropic drug use in ICU patients. Both benzodiazepines, antipsychotics and combined use of these agents could be associated with gender, age, disease severity, length of stay and reasons for admission. The time patterns we found in terms of length of stay give clues for further investigations in order to rationalise psychotropic drug use in the management of severely ill and complex patients. A limitation of this study was the fact that only complete days of use were included and that drugs prescribed 'as needed' were not included in the analysis. Therefore, the actual use was certainly higher than described here. Consequently, we recommend more detailed investigations of the prescription practice of psychotropics in the ICU with the collection of diagnostic data.

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CHAPTER 3.2

Correlated measures in longitudinal analysis of daily drug use patterns in a general intensive care unit

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ABSTRACT

In a previously published study (Chapter 3.1), we sought to identify determinants of psychotropic drug use in a retrospective case-control design. Therefore possible determinants of psychotropic drug use (gender, age, length of stay, reason for admission, disease severity) and psychotropic agents used (antidepressants, benzodiazepines, antipsychotics or benzodiazepines and antipsychotics concomitantly used) were retrospectively collected. Bed-days were used as unit of analysis and no corrections were made for correlated measures. The objective of the present study is to compare two different study designs to identify possible determinants of psychotropic drug use in an ICU. In a logistic regression analysis, odds rates were calculated for exposed days to psychotropics compared with non-exposed days. In order to adjust for correlated measures, or cluster effects through repeated measures in individual patients, logistic regression with a random effects model was performed. We found that adjustment for correlated measures did not result in major changes in the odds ratios. However, we did find that with more observations per cluster, adjustment for correlation has greater effect.

INTRODUCTION

In an earlier published study, we sought to identify determinants of psychotropic drug prescription in a retrospective case-control design [1]. In former studies it was concluded that the use of psychotropics in intensive care units (ICUs) is high compared to other non-psychiatric departments in a general hospital [2, 3]. In our previous study we found clear patterns of determinants of psychotropic drug use in ICU patients and both benzodiazepines, antipsychotics and combined use of these agents were associated with gender, age, disease severity, reason for admission and length of stay [1].

In order to cope with varying lengths of stay, we used bed-days as unit of analysis. Patients who used psychotropic drugs (cases) acted as their own controls because days exposed to psychotropics were compared to non-exposed days [1]. However, in this analysis no corrections were made for the fact that the observations were correlated.

The objective of the present study is to compare two different study designs to identify possible determinants of psychotropic drug use in an ICU. We will discuss the methodological considerations and pitfalls concerned with these methods.

MATERIAL AND METHODS

Study population and data

We retrospectively collected data over the first three months of 1995 from a consecutive sample of 137 patients of 18 years or over admitted to two general ICUs (17 beds in total) in the Netherlands with post-surgical and non-surgical severely ill patients. Patient data (gender, age, length of stay, disease severity, drug use during previous day and reason for admission) and psychotropics used (antidepressants, benzodiazepines, antipsychotics or benzodiazepines and antipsychotics concomitantly used) were extracted from the medical records by means of a standardised data collection form. Medication was coded according to the WHO Anatomical Therapeutic Chemical (ATC) coding system. Medication termed 'as needed' was not included in the analysis.

The Acute Physiologic and Chronic Health Evaluation (APACHE)-II classification system was used to classify patients according to severity of disease on admission [4]. This system uses a score (range 0-71) based on worst values during 24 hours of 12 routine physiologic measurements combined with age and previous health status to provide a standardised measure of severity of disease. This score has been validated and is correlated with subsequent risk on hospital death [4]. Patients were stratified according to APACHE-II scores into three categories: low (0-10), middle (11-20) and high (>21) severity of disease. Furthermore, patients were stratified according to reason for admission into: surgical ICU admission and other reasons, mostly severe internal diseases. Population and data have extensively been described before [1]. In addition, the variable 'drug use during previous day' was added which included drugs used during the day before the day under observation.

Study designs

Bed-days were taken as unit of analysis in order to cope with varying lengths of stay in the ICU. Non-24 hour admission days were excluded, effectively omitting the day of admission and discharge.

1) In a logistic regression analysis, we compared exposed days to psychotropics with non-exposed days and calculated odds ratios for various possible factors associated with exposed days. In this way, a single patient could contribute to both exposed and unexposed days. Adjustment for possible confounding was performed with exposed days as dependent variables and all possible factors associated with exposed days as independent variables.

2) In order to adjust for correlated measures, or cluster effects through the repeated measures in individual patients, we performed logistic regression with a random effects model. Again, exposed days were compared with non-exposed days, but here the patient-identifier was included as a random effect term. A logistic-binomial model was used to adjust for correlated measures and possible confounders. Data were analysed using EGRET and SPSS package.

Table 1. Basic characteristics of ICU patients (N = 137).

	Number of patients n (%)
Gender	
Female	55 (40.1)
Male	82 (59.9)
Age	
18-44	46 (33.6)
45-64	40 (29.2)
>65	51 (37.2)
APACHE-II score	
0-10	42 (30.7)
11-20	73 (53.3)
>21	20 (14.6)
missing value	2 (1.5)
Length of stay	
0-6	111 (81.0)
7-13	14 (10.2)
14-20	4 (2.9)
21-27	3 (2.2)
>28	5 (3.6)
Reason for admission	
Surgical	68 (49.6)
Non-surgical	69 (50.4)
Psychotropic drugs	
Benzodiazepines	49 (35.8)
Antipsychotics	24 (17.5)
Antidepressants	1 (0.7)

RESULTS

In Table 1 basic characteristics are shown. Mean age of the 137 patients was 54.1 years (range: 18-83 years). More male patients (59.9%) than female patients were admitted to the ICU. Mean APACHE score was 13.6 (median 13; range: 1-41) Mean length of stay of all patients was 5.4 days (median: 1 day; range: 0-82 days). The number of patients admitted for non-surgical reasons,

69 (50.4%), was equal to the number of patients admitted for surgical reasons. These non-surgical patients had the longest length of stay with a mean duration of 8.0 days (median: 2; range: 0-82) compared to surgical patients who had a mean length of stay of 2.7 days (median: 1; range: 1-23). We found that 49 patients (35.8%) used a benzodiazepine and 24 (17.5%) used an antipsychotic anytime during hospitalisation.

Table 2. Patient parameters associated with psychotropic drug use. Adjusted odds ratios with 95% confidence interval are compared in days of psychotropic use compared to days with no psychotropic drug use. Significant associations are printed in bold.

	Benzodiazepines only	Antipsychotics only	Benzodiazepines & antipsychotics
Gender			
Female	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male	1.7 (1.0-3.0)	5.2 (2.2-12.4)	0.8 (0.3-2.5)
Age			
18-44	1.0 (reference)	1.0 (reference)	1.0 (reference)
45-64	0.9 (0.4-2.0)	1.1 (0.3-3.9)	0.3 (0.1-1.2)
>65	0.7 (0.4-1.4)	1.0 (0.3-3.1)	0.4 (0.1-1.5)
Apache-II score			
0-10	1.0 (reference)	1.0 (reference)	1.0 (reference)
11-20	2.6 (1.0-6.8)	0.9 (0.3-3.1)	1.8 (0.3-8.7)
>21	2.7 (1.0-7.5)	0.5 (0.1-2.1)	1.8 (0.3-11.4)
Length of stay			
0-6	1.0 (reference)	1.0 (reference)	1.0 (reference)
7-13	0.7 (0.4-1.4)	1.7 (0.7-4.3)	1.2 (0.3-4.5)
14-20	0.8 (0.3-2.1)	4.5 (1.2-17.4)	4.4 (0.8-23.5)
21-27	0.4 (0.1-1.5)	0.8 (0.2-4.0)	1.8 (0.3-11.1)
>28	0.8 (0.4-1.5)	1.2 (0.4-3.1)	1.1 (0.3-4.0)
Drug use during previous day			
Benzodiazepine	11.8 (7.3-19.2)	2.2 (0.9-5.8)	21.0 (8.1-54.4)
Antipsychotic	0.5 (0.1-1.4)	23.2 (11.6-46.4)	29.7 (11.6-76.3)
Reason for admission			
Surgical	1.0 (reference)	1.0 (reference)	1.0 (reference)
Non-surgical	1.4 (0.8-2.6)	6.6 (2.1-20.1)	1.7 (0.4-7.0)

Table 2 shows adjusted odds ratios for patient parameters related to the number of days that benzodiazepines, antipsychotics or both were used. The 137 patients accounted for 734 bed-days. Male gender and APACHE-II score over 10 were significantly associated with the use of benzodiazepines. The use of antipsychotics was significantly more found in men, longer length of stay and a non-surgical reason for admission. Furthermore, using a benzodiazepine or antipsychotic during previous day was strongly associated with use of the same type of psychotropic or combined use of these drugs on the following day. Although not significant, previous benzodiazepine use was associated with higher risk on subsequent antipsychotic use and antipsychotic use with lower risk on subsequent benzodiazepine use with odds ratios of 2.2 (95% confidence interval: 0.9-5.8) and 0.5 (95% confidence interval (0.1-1.4).

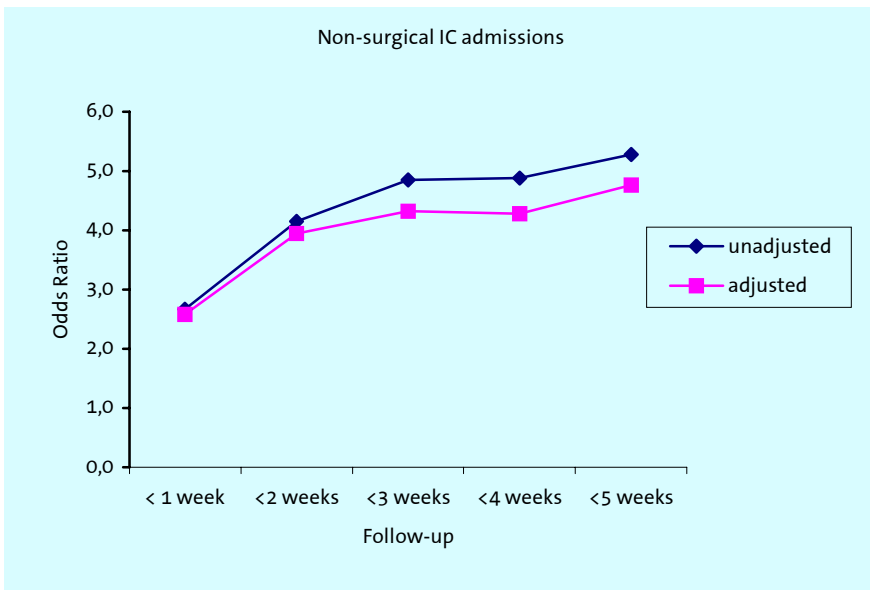
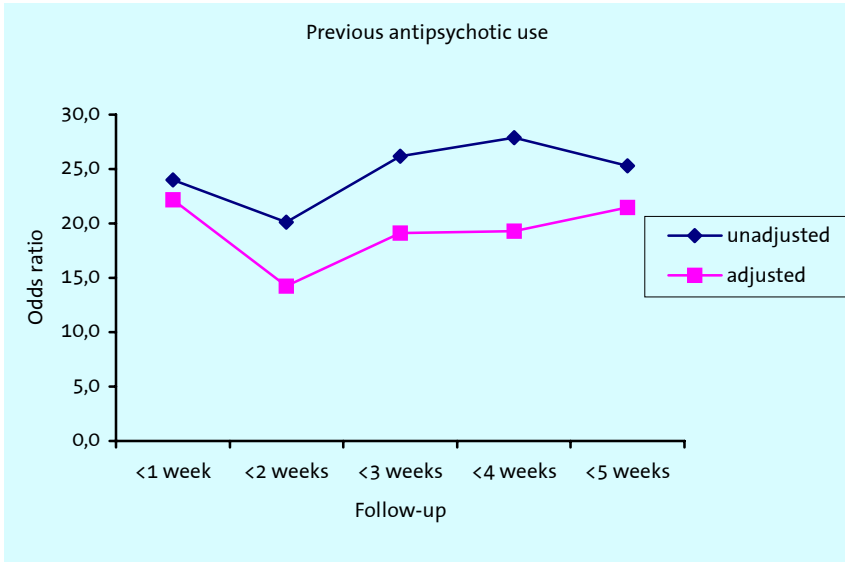
Table 3 shows patient parameters related to the number of days that benzodiazepines, antipsychotics or both were used, adjusted for possible confounding and in addition to Table 2 also for correlated measures. No major differences in the point-estimates of the odds ratios were found. However, confidence intervals were wider in most cases and less significant values were found.

In Figure 1 the effect of increasing number of observations per cluster on the logistic binomial model is illustrated with two examples. Figure 1a shows the effect on the odds ratio for use of antipsychotic drugs during the previous day on antipsychotic prescribing, while Figure 1b shows the same effect on the odds ratio for non-surgical admissions. Both graphs show an increased diverging with more measurements per cluster indicating a greater effect of adjusting for correlation with more observations.

Table 3. Days of psychotropic use compared to days with no use of psychotropics (presented as odds ratios with 95% confidence interval) adjusted for possible confounding and correlated measures in a logistic binomial model for distinguishable data with random effects. Significant associations are printed in bold.

	Benzodiazepines only	Antipsychotics only	Benzodiazepines & antipsychotics
Gender			
Female	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male	1.5 (0.8-2.9)	4.7 (1.6-14.0)	1.7 (0.2-12.6)
Age			
18-44	1.0 (reference)	1.0 (reference)	1.0 (reference)
45-64	0.8 (0.3-2.1)	1.0 (0.2-4.6)	0.2 (0.0-2.8)
>65	0.8 (0.3-1.7)	0.9 (0.2-3.5)	0.3 (0.0-2.9)
Apache-II score			
0-10	1.0 (reference)	1.0 (reference)	1.0 (reference)
11-20	2.4 (0.8-6.8)	0.9 (0.2-3.6)	2.0 (0.1-29.2)
>21	3.5 (1.1-11.0)	0.5 (0.1-2.6)	1.0 (0.0-19.9)
Length of stay			
0-6	1.0 (reference)	1.0 (reference)	1.0 (reference)
7-13	0.6 (0.3-1.2)	1.7 (0.6-4.5)	1.5 (0.3-8.4)
14-20	0.6 (0.2-1.9)	5.8 (1.0-34.5)	5.6 (0.5-58.5)
21-27	0.2 (0.0-1.2)	0.8 (0.1-4.8)	4.9 (0.2-109.8)
>28	0.5 (0.2-1.2)	1.8 (0.4-7.8)	1.0 (0.2-7.2)
Drug use during previous day			
Benzodiazepine	9.9 (5.8-16.8)	2.5 (0.9-7.0)	23.1 (5.2-102.7)
Antipsychotic	0.5 (0.1-1.5)	18.5 (7.6-45.0)	9.3 (1.8-48.9)
Reason for admission			
Surgical	1.0 (reference)	1.0 (reference)	1.0 (reference)
Non-surgical	1.3 (0.6-2.5)	5.3 (1.4-20.0)	2.2 (0.3-17.5)

Figure 1. Effects of increasing number of observations per cluster on the logistic binomial model.



DISCUSSION

The term 'repeated measures' refers to multiple observations of either exposure or outcome on the same sampling unit, often a patient or subject [5]. Often these observations within the same subject will be correlated and this has to be taken into account when analysing these data. However in pharmacoepidemiological studies, possible intra-subject correlation is often not taken into account. With more and more longitudinal databases available for observational research, the progress in measurement of exposure patterns over time, and the availability of outcomes measures on detailed patient level, the number of studies involving repeated measures is increasing.

In a study we performed on determinants of psychotropic drug use in patients admitted to an intensive care unit in a general hospital we had data available on the drug exposure for each day during admission as well as data on a patient-level [1]. We considered each patient-day as an independent observation and subsequently looked at days with psychotropic drug use (cases) and compared them to days without psychotropic drug use (controls) in a logistic regression model. In the present study, we took the correlation that is to be expected between the repeated measures within the same patient into account and compared the two methods. We found no major differences in the point estimators of the odds ratios between the two methodologies used. However, the confidence intervals after adjustment for correlated measures were considerably wider in most cases resulting in a loss of statistical significance. It is to be expected that adjustment for correlated measures has a bigger effect when more observations per cluster are present. We simulated this in our data by stratifying for length of follow-up, or in other words number of patient-days contributed to the dataset. We saw an increase in the effect of adjustment for correlation with increasing number of observations per patient included in the model. Adjustment for correlation seems to be especially pertinent with multiple observations per subject.

In the present study, in addition to the above mentioned methodological considerations and in addition to the former study [1], we found that previous benzodiazepine and antipsychotic use were significantly associated with psychotropic use during the following day. Apparently critically ill patients

admitted on the intensive care setting need psychotropics for longer periods of time. Although not significant, the association of previous benzodiazepine use with higher risk on antipsychotic use the following day and the association of previous antipsychotic use with lower risk on benzodiazepine use the following day suggests that during critical illness in patients who need sedation, physicians consider benzodiazepines as first choice and the use of antipsychotics or combined use of benzodiazepines and antipsychotics as second. It is likely that benzodiazepines are used for a basic level of sedation. In the ICU, many risk factors in the patient and pharmacological and environmental risk factors of delirium are seen [6]. After a few days in this setting patients may develop a delirium [7]. Antipsychotics are the cornerstone in its treatment [6].

In conclusion, we have shown that adjustment for correlated measures in data with many observations per patient is feasible and relatively simple to perform. Although in this study, adjustment did not result in major changes in the odds ratios found, we did find that with more observations per cluster, adjustment for correlation has greater effect.

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CHAPTER 4

Psychotropic drug use in settings for people with intellectual disabilities

- 4.1 Psychotropic drug use in intellectually disabled group home residents with behavioural problems
- 4.2 Determinants of multiple psychotropic drug use in patients with mild intellectual disabilities or borderline intellectual functioning and psychiatric or behavioural disorders

CHAPTER 4.1

Psychotropic drug use in intellectually disabled group home residents with behavioural problems

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ABSTRACT

Little is known about psychiatric and behavioural factors associated with psychotropic drug use in settings for people with intellectual disabilities. The aim of this study was to measure the point prevalence of psychotropic drug use in a problem behaviour group (PBG) consisting of intellectually disabled residents of group homes compared to a random group (RG) and to gain insight in possible factors that are associated with group membership. From all group homes in the Netherlands, 573 problematic residents were selected by staff (one resident from each home) and 1479 residents were randomly sampled from all the homes. Mental health problems were measured using the Reiss Screen for Maladaptive Behavior and the Psychopathology Instrument for Mentally Retarded Adults. Psychotropics (excluding anticonvulsants) were used by 52.6% of the PBG and by 22.8% of the RG. Young age, psychotic, anxiety and aggression symptoms were significantly associated with the PBG as was the use of antipsychotics and antidepressants. A low prevalence of antidepressants or mood stabilisers, antipsychotics and anxiolytics was found in residents with affective, psychotic, or anxiety symptoms. It is likely that the group home staff finds it difficult to deal with socially disruptive behaviour. Our findings suggest that a considerable number of residents with psychiatric or behavioural symptoms are undertreated.

INTRODUCTION

Although studies on mental health problems among people with intellectual disabilities vary greatly in sampling and identification techniques [1] there is a consensus that people with intellectual disabilities are at higher risk of mental health problems than people from the general population [1-5].

Because of complicated behavioural problems in this population, psychotropic drug therapy is often attempted, but is suspected to interfere with cognitive and behavioural skills [6]. Nevertheless, prevalence rates of psychotropic and/or anticonvulsant drug use among persons with intellectual disabilities are high, ranging from 44 to 60% in institutional populations and from 35 to 45% in community settings [7]. According to a recent Dutch survey, psychotropic agents including anticonvulsants were prescribed to 41% of an institutionalised population and to 29% of group home residents. Overall, antipsychotic agents were prescribed to 17.5%, anxiolytics to 6.8%, antidepressants to 3.6% and anticonvulsants to 18.4% of the total sample [8].

Little is known about psychiatric and behavioural factors associated with the prescription of psychotropic drugs and how appropriately these drugs are prescribed in settings for people with intellectual disabilities [9]. Examining the relation between psychiatric diagnosis and medication regime in a group of 242 institutionalised people with intellectual disabilities and psychiatric disorders, 55% of the diagnosis-medication combinations were found to be either uncertain or probably inappropriate [10]. According to a more recently published review, many people receiving psychotropic agents had no psychiatric diagnosis in their case files and medication was sometimes prescribed without any specific target symptom or diagnosis [11].

The present study was designed to measure the point prevalence of psychotropic drug use in intellectually disabled group home residents with problem behaviour. Furthermore, we wanted to gain insight into this group of residents by analysing the possible factors associated with the problem behaviour group.

MATERIALS AND METHODS

Setting

In the Netherlands, the term 'group home' refers to a multitude of community-based settings, ranging from houses with over 20 residents (living in three to four units) to annexes of these houses where fewer persons reside, sometimes only two or three. In contrast to the larger group home, the employees are not continuously present in the annexes. If possible, residents of group homes make use of general health care facilities. All group home residents have mild or moderate intellectual disabilities. In total, there are 573 group homes in the Netherlands that house 15,622 persons with intellectual disabilities

Subjects

The staff in each group home was instructed to select one resident they considered as having the most severe behavioural problems for the problem behaviour group (PBG). A random group (RG) of 1479 residents with intellectual disabilities was drawn up by selecting every ninth resident from a random list in each group home [12]. As a consequence of this method, larger group homes provided more residents for the RG.

Procedure

Information on residents was collected in 1996 using a questionnaire to be completed by the staff. The questionnaire included the following topics: gender, age, previous mental health care and somatic disorder or handicap. Mental health problems were measured with the Dutch versions of the Reiss Screen for Maladaptive Behavior and the Psychopathology Instrument for Mentally Retarded Adults (PIMRA). Information on the current use of psychotropic drugs were recorded in terms of type and daily dosage.

Psychotropic agents

Psychotropic drugs were mainly prescribed by general practitioners. Psychotropic use was coded according to the WHO Anatomical Therapeutic Chemical (ATC) coding system. Actual daily exposure to psychotropics (antipsychotics, anticholinergics, antidepressants, anxiolytics, hypnotics / sedatives, antihistamines -promethazine- and anticonvulsants) was converted into the number of Defined Daily Dosages (DDD-equivalents), a standardised

technical unit of measurement, defined as the average dose per day for a drug used for its main indication in adults [13].

Instruments

The Dutch versions of the Reiss Screen for Maladaptive Behavior [14] and the Psychopathology Instrument for Mentally Retarded Adults (PIMRA) [15] were used for measuring mental health problems.

The Reiss Screen for Maladaptive Behavior

The Reiss Screen for Maladaptive Behavior is a questionnaire for informants developed to assess the risk of mental health problems among persons with mental retardation [16]. It consists of 35 items describing problem behaviour resulting in a total score indicative of general mental health. The Reiss Screen has eight subscales: psychosis, aggression, autism, paranoia, depression behavioural signs, depression physical signs, dependent disorder and avoidant personality disorder, each resulting in a subscale score. The Dutch version has good internal consistency for the total score with a Cronbach's alpha of .90 and moderate reliability for most subscales, ranging from .50 (autism) to .85 (aggression) [17].

Psychopathology Instrument for Mentally Retarded Adults

This instrument is based on DSM-III-R and consists of 56 items in eight subscales: schizophrenia, affective disorders, psychosexual disorders, adaptation disorders, anxiety disorders, somatoform disorders, personality disorders and inadequate (social) adaptation (not a DSM-III-R classification) [18]. Two versions were developed: a self report version and an informant version, which was used in this study. All PIMRA subscales consist of seven items (symptoms), four of which must be present for the disorder to be diagnosed [18]. The Dutch version of the PIMRA has good internal consistency for the total score (.90) with subscale reliabilities ranging from .46 (personality disorder) to .81 (somatoform disorder) [19].

Behavioural and psychiatric symptoms

To gain insight into intellectually disabled group home residents with problem behaviour, four groups of symptoms were selected: affective, psychotic, anxiety

and aggression symptoms. Because there are no conclusive studies regarding the validity of the subscales of the Reiss Screen and the PIMRA, scale scores must be interpreted with caution. On basis of these instruments, we could not establish a diagnosis in terms of DSM-IV or ICD-10. Additionally, drugs are often prescribed for target symptoms in this population, not for disorders. Therefore, we will present the mental health problems in terms of symptoms.

In the Results section, residents were considered to have affective symptoms when they were positive for two of the three depression subscales (behavioural and physical signs for depression according to the Reiss Screen and affective disorder according to the PIMRA). Residents positive for two of the three psychosis subscales (psychosis and paranoia according to the Reiss Screen and schizophrenia according to the PIMRA) were considered as people with psychotic symptoms. Residents had aggressive symptoms if they scored above the cut-off in the similar Reiss Screen subscale. Where residents scored above the cut-off in the anxiety disorder subscale of the PIMRA, they were considered as having symptoms.

Analysis

Using logistic regression analysis, we compared the PBG with the RG and calculated prevalent odds ratios for various possible factors associated with the PBG including gender, age, affective, psychotic, anxiety and aggression symptoms and psychotropic drug use. Adjustment for possible confounding was performed with the PBG as dependent variable and all possible factors associated with the PBG as independent variables.

We used the Statistical Package for the Social Science [20] to analyse the data.

RESULTS

The response rate for the PBG was 68.9% (395 returned questionnaires) and 71.7% (1.061 returned questionnaires) for the RG. The mean age of residents in the PBG was 39 years (SD: 11.8) and this was 42 years (SD: 13.4) in the RG. The prevalence of people with Down's syndrome was 6.1% in the PBG and 14.8% in the RG. In the PBG, 8.2% had experienced seizures in the past and a similar percentage of 7.3% was identified in the RG. 70.4% of the PBG had previous

contact with the mental health services, the figure being 18.5% for the RG. Anxiety and aggression symptoms were most prevalent in the PBG. Of these residents, 52.9% and 43.1% suffered from these symptoms, compared to 22.0% and 4.9% in the RG. 39.2% of the PBG suffered from more than one type of symptom in contrast to 7.0% in the RG

Table 1. Gender, age, psychiatric-/behavioural symptoms and psychotropic agents associated with the problem behaviour group (PBG) (n = 395*) compared to the random group (RG) (n = 1061*). Crude odds ratios and adjusted odds ratios calculated with 95% confidence interval (95% CI). Significant associations are printed in bold.

	PBG n (%)	RG n (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Male	213 (54.1)	521 (49.3)	0.8 (0.7-1.0)	0.8 (0.6-1.1)
Age group (years)				
18-35	172 (44.7)	337 (32.2)	1.0 (reference)	1.0 (reference)
36-50	149 (38.7)	437 (41.7)	0.7 (0.5-0.9)	0.8 (0.5-1.1)
51-65	58 (15.1)	207 (19.8)	0.6 (0.4-0.8)	0.5 (0.3-0.7)
>=66	6 (1.6)	67 (6.4)	0.2 (0.1-0.4)	0.3 (0.1-0.7)
Psychiatric/behavioural symptoms**				
Affective symptoms	98 (26.3)	64 (6.4)	5.2 (3.7-7.4)	1.2 (0.7-2.1)
Psychotic symptoms	80 (21.3)	22 (2.2)	12.1 (7.3-20.4)	2.6 (1.4-5.0)
Anxiety symptoms	202 (52.9)	224 (22.0)	4.0 (3.1-5.1)	1.9 (1.4-2.7)
Aggression symptoms	163 (43.1)	50 (4.9)	14.6 (10.2-21.1)	10.0 (6.6-15.2)
Psychotropic drugs				
Antipsychotic	159 (41.2)	175 (16.7)	3.5 (2.7-4.6)	2.1 (1.4-3.1)
Antidepressant	59 (15.3)	48 (4.6)	3.8 (2.5-5.7)	2.4 (1.5-3.7)
Anxiolytic	60 (15.5)	65 (6.2)	2.8 (1.9-4.1)	1.3 (0.8-1.9)
Anticonvulsant	83 (21.5)	167 (15.9)	1.4 (1.1-2.0)	0.9 (0.7-1.2)

* In most analyses the n was slightly smaller due to missing values.

** Psychiatric/behavioural symptoms: 1) Affective symptoms: positive for 2 of 3 depression subscales (depression behavioural signs and depression physical signs of the Reiss Screen and affective disorder of the PIMRA). 2) Psychotic symptoms: positive for 2 of 3 psychosis subscales (psychosis and paranoia of the Reiss Screen and schizophrenia of the PIMRA). 3) Anxiety symptoms: positive for the anxiety disorder subscale of the PIMRA. 4) Aggression symptoms: positive for the aggression subscale of the Reiss Screen.

Table 1 reveals the prevalence rates of patient characteristics and the associations between these characteristics and group membership (PBG or RG). Pipamperone, a serotonin-2/dopamine-2 antagonist and thioridazine, were the most frequently used antipsychotic drugs in both groups. In the PBG, pipamperone was prescribed to 31.4% of antipsychotic users and to 20.9% of all psychotropic users and thioridazine to 17.6% and 11.7%. In the RG, pipamperone was used by 17.7% of antipsychotic users and by 8.9% of all psychotropic users, thioridazine by 14.9% and 7.4%, respectively. Young age, psychotic symptoms, anxiety symptoms and aggression symptoms were found to be significantly associated with the PBG. Antipsychotics and antidepressants were significantly more prescribed in the PBG.

Table 2. Prevalence of psychotropic drug use in the PBG (n = 395*) and the RG (n = 1061*).

	PBG n (%)	RG n (%)
Psychotropic drugs		
Including anticonvulsants	239 (61.8)	349 (33.2)**
Excluding anticonvulsants	203 (52.6)	240 (22.8)**
Number of drugs used		
1	107 (27.7)	170 (16.2)**
2	65 (16.8)	102 (9.7)**
3	43 (11.1)	59 (5.6)**
>=4	24 (6.2)	18 (1.7)**
Number of drug categories used		
1	123 (31.9)	223 (21.3)**
2	73 (18.9)	97 (9.2)**
3	32 (8.3)	28 (2.7)**
>=4	11 (2.8)	1 (0.1)**

* In most analyses the n was slightly smaller due to missing values.

**p-value <0.05 PBG compared to the RG.

Table 2 shows prevalence rates of psychotropic drug use. In the PBG, 61.8% of the residents used a psychotropic agent, in contrast to 33.2% in the RG. These prevalence rates were 52.6% and 22.8% with anticonvulsants left out. The prevalence of residents using three or more drugs in the PBG was 17.3%, whereas 7.3% of the RG used three or more drugs. People using psychotropic drugs of three or more drug categories (antipsychotics, anticholinergics, antidepressants, anxiolytics, hypnotics/sedatives, antihistamines and anticonvulsants) of the PBG (11.1%) outnumbered people of the RG using drugs of three or more drug categories (2.8%).

The lowest dosages were found in the antipsychotic group with a mean dosage of levomepromazine of 0.2 DDD (SD: 0.1) in the PBG and 0.1 DDD (SD: 0.1) in the RG. More potent antipsychotics were used in higher dosages. For example, the mean dosage of haloperidol in the PBG was 0.7 DDD (SD: 0.6) and 0.6 DDD (SD: 0.6) in the RG.

Table 3. Number of residents using a psychotropic drug calculated for different symptom clusters in the PBG (n = 395) and the RG (n = 1061). Mental health problems were measured by using Dutch versions of the Reiss Screen for maladaptive behavior and the PIMRA.

	Affective symptoms*		Psychotic symptoms**		Anxiety symptoms†	
	n (%)		n (%)		n (%)	
	PBG n = 98	RG n = 64	PBG n = 80	RG n = 22	PBG n = 202	RG n = 224
Antidepressants	28 (28.6)	10 (15.6)	17 (21.3)	3 (13.6)	41 (20.3)	19 (8.5)
Antipsychotics	58 (59.2)	26 (40.6)	42 (52.5)	10 (45.5)	107 (53.0)	69 (30.8)
Anxiolytics	26 (26.5)	13 (20.3)	18 (22.5)	2 (9.1)	43 (21.3)	24 (10.7)
Hypnotics/sedatives	11 (11.2)	1 (1.6)	7 (8.8)	0 (0)	12 (5.9)	3 (1.3)
Anticonvulsants	20 (20.4)	10 (15.6)	21 (26.3)	4 (18.2)	41 (20.3)	41 (18.3)

*Positive for 2 of 3 depression subscales (depression behavioural signs and depression physical signs of the Reiss Screen and affective disorder of the PIMRA).

**Positive for 2 of 3 psychosis subscales (psychosis and paranoia of the Reiss Screen and schizophrenia of the PIMRA).

†Positive for the anxiety disorder subscale of the PIMRA.

In order to gain more insight into the use of medication, prevalence rates of drugs calculated for affective, psychotic and anxiety symptoms are shown in Table 3. Antipsychotics were the most frequently prescribed agents in both groups. In the PBG, 28.6% of the patients with affective symptoms used antidepressants. In the RG, 15.6% of the patients with affective symptoms used these drugs. Antipsychotics were prescribed in 52.5% of the patients with psychotic symptoms in the PBG, compared to 45.5% of the patients in the RG. Residents with anxiety symptoms from the PBG more often used anxiolytics (21.3%) than residents from the RG with anxiety symptoms (10.7%).

DISCUSSION

The present study involving 1456 intellectually disabled group home residents showed, as expected, that psychotropic drug use was much higher in problematic group home residents than in the random study group. We hypothesise that the administration of psychotropic drugs, especially antipsychotics, is often the result of difficulties in dealing with problematic residents. Furthermore, it is likely that considerable numbers of residents with psychiatric or behavioural symptoms are undertreated.

We found that 61.8% of the PBG compared to 33.2% of the RG used at least one psychotropic agent including anticonvulsants and 52.6% compared to 22.8% excluding anticonvulsants. This high use in the PBG is consistent with the findings of Jacobson [21], who found an even higher prevalence rate (70.8%) of psychotropic drug use (excluding anticonvulsants) in residents with psychiatric disorders living in community care facilities. High prevalence rates are not surprising since the use of psychotropic drugs is one of the mainstay strategies in coping with behavioural and psychiatric problems. The high use of antipsychotics and the low use of antidepressants of 41.2% and 15.3% of the PBG and 16.7% and 4.6% of the RG tallies with other studies, although varying prevalence rates for different samples from community-based facilities have been found [9, 11, 22].

We observed a tendency to prescribe antipsychotic agents in dosages below 1 DDD in the PBG and the RG. One reason for this could be the reports of

beneficial effects from using low dosages of antipsychotic agents in intellectually disabled people with behavioural disorders [23].

In this study, the response rate was approximately 70% for both the problem behaviour group (PBG) and the random group (RG). Although we did not collect data from the non-responders, the differences in comparing demographic data from our sample to the data from the Dutch registration of all group home residents were relatively minor. It is therefore likely that our results are representative of the total population of group home residents. However, selection bias may have been introduced by letting staff select the subjects for the PBG on their own. This would be the case if the staff had selected a resident for the PBG according to psychotropic medication use. Although we cannot rule out this possibility, we instructed staff specifically to look at problematic behaviour and we did not find any evidence that they did not follow these instructions.

Subjects in the PBG were younger and had psychotic, anxiety or aggression symptoms more often. Apparently, the staff found it difficult to deal with this group since they chose these residents for the PBG. This is emphasised by the high prevalence of antipsychotics, often prescribed in low dosages and for a broad spectrum of indications and multiple drug therapy in the PBG. It also tallies with the results from other studies involving people with intellectual disabilities, in which an association was found between socially disruptive behaviour and the prescription of antipsychotics [24, 25]. Heavy use of antidepressants in the PBG compared to the RG may be explained by the fact that antidepressants, mainly SSRIs, are sometimes prescribed for people with poor impulse control or self-injurious behaviour [26].

There is much evidence for the treatment of mood, psychotic, or anxiety disorders with antidepressants or mood stabilisers, antipsychotics and anxiolytics [26-29]. Nevertheless, we found a low prevalence of these agents in subjects with the corresponding symptoms. This finding suggests that a considerable number of residents with psychiatric or behavioural symptoms is undertreated. It is most likely that residents' symptoms were not detected due to atypical presentation, difficulties in obtaining information and/or limited

access to psychiatric services [30]. It is also possible that, before resorting to medication, psychotherapeutic techniques were used to treat the symptoms.

In conclusion, we found considerable differences in the prevalence rates of psychotropic drugs between a PBG and a RG of group home residents with a high prevalence of antipsychotics. It is likely that low dosages of antipsychotics as well as a broad spectrum of drugs were often used for treating socially disruptive behaviour, as was indicated by the association between psychotic and aggression symptoms and group membership. Our findings suggest that a considerable number of residents with psychiatric or behavioural symptoms were undertreated. In order to determine causal relations between symptoms and treatment, our findings should be confirmed in another study design with the data collection on the effectiveness of drug use.

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CHAPTER 4.2

Determinants of multiple psychotropic drug use in patients with mild intellectual disabilities or borderline intellectual functioning and psychiatric or behavioural disorders

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ABSTRACT

Prevalence rates of psychotropic drug use in people with intellectual disabilities are high and pharmacotherapy is often attempted with multiple drugs. The presence of disruptive behaviour is an important factor associated with the use of psychotropic drugs in this population. We wanted to gain insight into prevalence and determinants of multiple psychotropic drug use among patients with mild intellectual disabilities or borderline intellectual functioning with psychiatric- or behavioural disorders. Therefore, data on psychotropics and possible determinants of use were retrospectively collected during 1992-1997 in a specialised closed ward of a Dutch general psychiatric hospital. We defined multiple drug use as concomitant prescription (regular and/or as needed) of a combination of benzodiazepines/tranquillisers/antipsychotics/anticonvulsants /antidepressants. Multiple drug use, seen in 48% of the patients, was associated with a long duration of stay, psychosis, aggressive-, bizarre-, attention seeking behaviour and involuntary measures. We conclude that it is likely that difficulties in the management of socially disruptive behaviour are often countered by multiple drug prescription.

INTRODUCTION

Studies on the prevalence of mental disorders in people with intellectual disabilities have shown higher rates than those found in the general population [1-5]. Recurrent crises because of aggressive and other disruptive behaviours are strongly associated with psychotropic drug use [6] and pharmacotherapy is often attempted with multiple drugs in this population [7]. In two recent surveys the prevalence of the use of more than one psychotropic drug ranged from 10,7% of 1101 residents of over 120 group homes in the U.S. to about a quarter of 520 adults living in institutions or community based settings in the U.K. [8, 9]. Multiple drug use may be in some cases appropriate but can also be reason for concern in other cases because the more drugs a patient uses the greater the risk on frequent and serious untoward interactions and side-effects which can interfere with cognitive and behaviour skills [10, 11].

We performed a retrospective study into the prevalence of multiple psychotropic drug use in patients with mild intellectual disabilities or borderline intellectual functioning and psychiatric- or behavioural disorders admitted to a specialised closed ward of a psychiatric hospital. Furthermore we wanted to gain insight into multiple drugs by analysing possible determinants of use.

MATERIALS AND METHODS

Patients and data collection

Data were retrospectively collected over the years 1992-1997 from a consecutive sample of 105 patients of 16 years or older concerning their first admission to a specialised closed ward for people with mild intellectual disabilities or borderline intellectual functioning and psychiatric- or behavioural disorders. Patient data (gender, age, level of intellectual functioning, psychiatric diagnosis, behavioural diagnosis, application of involuntary measures, duration of stay) and data on the use of psychotropics (type of medication - benzodiazepines, tranquillisers including droperidol, levomepromazine and promethazine, antipsychotics, anticholinergics, anticonvulsants, antidepressants and lithium-, dosage, duration of treatment) were extracted from the medical records by means of a standardised data collection form. The study

protocol was approved by the Ethics Committee of the University Medical Center Utrecht.

The ward

The closed ward is part of a general psychiatric hospital and has 24 beds. It serves an area of four million people coming from the west and middle regions of the Netherlands. Almost all patients have long histories of recurrent admissions to psychiatric hospitals or to specialised units of residential settings. The primary purpose of the ward is to establish a psychiatric- or behavioural diagnosis and improve the behaviour by prolonged treatment and rehabilitation.

Psychiatric and behavioural diagnosis

Psychiatric diagnoses according to DSM-III-R/-IV criteria were made during the first month of hospitalisation by the psychiatrist (MGMC) of the unit. Additionally, reasons for admission were classified into six categories of behavioural diagnoses: antisocial-, aggressive- (including selfmutilation- and suicidal behaviour), withdrawal-, sexually unacceptable-, bizarre- and attention seeking behaviour.

As a proxy for destructive behaviour during hospitalisation we used the number of days on which involuntary measures, mostly seclusion, were taken.

Use of psychotropic medication

Multiple drug use was defined as concomitant prescription (regular or as needed) of: 1) two antipsychotics, 2) antipsychotic and anticonvulsant, 3) antidepressant and anticonvulsant, 4) antidepressant and antipsychotic, 5) tranquilliser and benzodiazepine and antipsychotic, 6) tranquilliser and benzodiazepine and anticonvulsant and 7) tranquilliser and benzodiazepine and antidepressant. Combinations with anticonvulsants were taken into account because these agents are often prescribed for psychiatric- or behavioural disorders in this population. Combinations with anticholinergics were not taken into account because the addition of these agents to antipsychotic agents is common because of extrapyramidal side-effects.

During the first month of hospitalisation patients are usually observed for diagnostic purposes and new treatments based on the results of these

observations start after this period. Medication used during the first month was often a continuation of the medication prescribed by the referring physician. Therefore we defined psychotropic drugs during hospitalisation by excluding drugs only used during this month.

Medication was coded according to the WHO Anatomical Therapeutic Chemical (ATC) coding system. Daily exposure to psychotropics was standardised in number of Defined Daily Doses (DDD-equivalents), a standardised technical unit of measurement defined as the average dose per day for a drug used for its main indication in adults [12]. As needed medication was also included in the analysis.

Analysis

In a nested case-control analysis we compared patients exposed to multiple psychotropic drugs with patients not exposed to multiple psychotropic drugs and calculated odds ratios for various possible determinants including gender, age, level of intellectual functioning, psychiatric diagnosis, behavioural diagnosis, application of involuntary measures and duration of stay. Adjustment for possible confounding was performed by an unconditional logistic regression analysis with multiple drug status as the dependent variable and possible determinants as independent variables. All analyses were performed with SPSS package and EGRET.

RESULTS

The study population consisted of 96 patients with a duration of stay of more than one month. Nine patients with a hospitalisation shorter than one month were excluded. The patients were predominantly young with a mean age of 26.6 years ranging from 16 to 57 years and a median of 24 years. Male patients (71.9%) outnumbered female patients. Patients with borderline intellectual functioning comprised 45.8%, patients with mild intellectual disabilities 49.0% and patients with moderate intellectual disabilities 5.2% of the population. Of 76 patients data on discharge were available. The remaining 20 were still hospitalised at the end of the follow-up. The mean length of stay of all 76 patients with completed hospitalisations at the end of the study was 388.3 days ranging from 38 to 1,734 days with a median of 270.5 days. Patients using regular or as needed psychotropic drugs during hospitalisation had an average

length of stay of 435.5 days ranging from 38 to 1,734 days with a median of 295 days whereas the average length of stay for patients using no psychotropic drugs was 196.6 days, ranging from 47 to 538 days with a median of 128 days.

Table 1. Prevalence of regular psychotropic drug use at the first day of stay (referral medication), during stay and at the day of discharge. At admission and discharge, point prevalence rates were calculated and during stay the period prevalence was estimated. Of 76 of 96 patients data on discharge were available.

	Referral medication (n = 96) n (%)		Medication during stay (n = 96) n (%)		Medication at discharge (n = 76) n (%)	
	Number of patients	Average daily dose*	Number of patients	Average daily dose*	Number of patients	Average daily dose*
Antipsychotics	49 (51.0)	1.3	64 (66.7)	1.1	42 (55.3)	1.4
Benzodiazepines	30 (31.3)	1.5	53 (55.2)	1.4	33 (43.4)	1.2
Tranquillisers	11 (11.5)	1.3	20 (20.8)	2.2	10 (13.2)	2.2
Antidepressants	13 (13.5)	1.2	25 (26.0)	1.1	6 (7.9)	0.8
Lithium	1 (1.0)	**	4 (4.2)	**	2 (2.6)	**
Anticonvulsants	12 (12.5)	1.8	18 (18.8)	1.4	10 (13.2)	1.3
Anticholinergics	19 (19.8)	0.7	27 (28.1)	0.7	12 (15.8)	0.8

*Number of DDD-equivalents.

**Lithium has no DDD.

Table 1 shows data on the regular use of psychotropic agents. At admission and discharge point prevalence rates were calculated. During stay the period prevalence was estimated. At admission 63.5% of the patients used psychotropic drugs including anticonvulsants, during stay 79.2% and at discharge 69.7%. Antipsychotics and benzodiazepines were most frequently used. Pipamperone was the most commonly prescribed antipsychotic and was used by 19 (19.8%) of all patients and 29.7% of all antipsychotic consumers during stay. Oxazepam was the most frequently prescribed benzodiazepine, used by 32 (33.3%) of all patients and 60.4% of benzodiazepine users. Antipsychotics were prescribed in the widest dose range from 0.1 (thioridazine) to 2.7 DDD-equivalents per day (haloperidol). In 46 patients (47.9%) multiple drugs were prescribed during stay. Of the multiple drug users, nine used an anticonvulsant from which five had a diagnosis of seizure disorder.

Table 2. Patient parameters and multiple psychotropic drug use*---Adjusted odds ratios calculated with 95% confidence interval (95% CI). Significant associations are printed in bold.

	Multiple drug users (n = 46) n (%)	No multiple drug users (n = 50) n (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Gender				
Male	31 (67.4)	38 (76.0)	1.0 (reference)	1.0 (reference)
Female	15 (32.6)	12 (24.0)	1.5 (0.6-3.8)	1.8 (0.5-6.8)
Age (years)				
16-20	10 (21.7)	11 (22.0)	1.0 (reference)	1.0 (reference)
20-30	22 (47.8)	23 (46.0)	1.1 (0.4-3.0)	0.9 (0.2-3.6)
>=30	14 (30.4)	16 (32.0)	1.0 (0.3-2.9)	0.7 (0.1-3.4)
Duration of stay (months)				
1-6	12 (26.1)	23 (46.0)	1.0 (reference)	1.0 (reference)
6-12	11 (23.9)	10 (20.0)	2.1 (0.7-6.4)	1.3 (0.2-7.1)
>=12	23 (50.0)	17 (34.0)	2.6 (1.0-6.6)	2.0 (0.6-6.5)
Intellectual functioning				
Borderline	18 (39.1)	26 (52.0)	1.0 (reference)	1.0 (reference)
Mild/moderate	28 (60.9)	24 (48.0)	1.7 (0.7-3.8)	1.5 (0.4-4.9)
Psychiatric diagnosis				
Psychotic dis.	17 (37.0)	5 (10.0)	5.3 (1.8-15.9)	13.2 (2.3-74.8)
Personality dis.	9 (19.6)	11 (22.0)	1.0 (0.4-2.6)	2.4 (0.5-10.8)
Substance related dis.	5 (10.9)	4 (8.0)	1.4 (0.4-5.6)	2.4 (0.3-18.6)
Impulse control dis.**	10 (21.7)	17 (34.0)	0.5 (0.2-1.2)	1.3 (0.3-6.1)
Behavioural diagnosis				
Antisocial behav.	9 (19.6)	16 (32.0)	0.5 (0.2-1.3)	0.7 (0.1-3.2)
Aggressive behav.	33 (71.7)	26 (52.0)	2.3 (1.0-5.5)	7.1 (1.9-27.4)
Withdrawal behav.	7 (15.2)	6 (12.0)	1.3 (0.4-4.3)	2.8 (0.4-18.8)
Sex. unaccept. Behav.	6 (13.0)	9 (18.0)	0.7 (0.2-2.1)	1.7 (0.3-8.2)
Bizarre behav.	9 (19.6)	2 (4.0)	5.8 (1.2-28.7)	15.3 (1.7-137.7)
Attent. seeking behav.	12 (26.1)	8 (16.0)	1.9 (0.7-5.0)	4.4 (0.9-21.1)

*Multiple drug use: 1) two antipsychotics, 2) antipsychotic and anticonvulsant, 3) antidepressant and anticonvulsant, 4) antidepressant and antipsychotic, 5) tranquilliser and benzodiazepine and antipsychotic, 6) tranquilliser and benzodiazepine and anticonvulsant and 7) tranquilliser and benzodiazepine and antidepressant.

**Included are: attention deficit- and disruptive behaviour disorders and impulse control disorders not elsewhere classified.

In Table 2 determinants of multiple psychotropic drug use are listed. Psychotic disorder, aggressive behaviour and bizarre behaviour were significantly associated with multiple psychotropic drug use. Attention seeking behaviour was also associated with multiple drug use, although not statistically significant as was the association with duration of stay. Since we were interested in determinants of multiple psychotropic drug use we looked at involuntary measures taken on days before multiple drug prescription. Only patients using multiple drugs after the first week of admission (27) were entered into this analysis. Involuntary measures were associated with multiple drug use with an odds ratio of 2.3 (95% confidence interval: 0.7-8.4) (Table 3).

Table 3. Involuntary measures -in percentages of days foregoing multiple drug use- and multiple drug use* after the first week of admission. Odds ratios are calculated with 95% confidence interval (95% CI).

	Multiple drug users (n = 27) n (%)	No multiple drug users (n = 50) n (%)	Odds Ratio (95% CI)
Involuntary measures			
No measures	18 (66.7)	41 (82.0)	1.0 (reference)
Measures < 10%	3 (11.1)	5 (10.0)	0.7 (0.2-3.2)
Measures > 10%	6 (22.2)	4 (8.0)	2.3 (0.7-8.4)

*Multiple drug use: 1) two antipsychotics, 2) antipsychotic and anticonvulsant, 3) antidepressant and anticonvulsant, 4) antidepressant and antipsychotic, 5) tranquilliser and benzodiazepine and antipsychotic, 6) tranquilliser and benzodiazepine and anticonvulsant and 7) tranquilliser and benzodiazepine and antidepressant.

DISCUSSION

In the present study, we found that during their hospital stay approximately 80% of the patients used one or more psychotropics including anticonvulsants with highest use of antipsychotics, prescribed to 66.7%. The use of psychotropics was high compared to other studies among people with intellectual disabilities in institutions in which prevalence rates from 44 to 60% were found [13]. When anticonvulsants were excluded only slightly lower prevalence rates were found. High prevalence rates are not surprising because

prerequisites for admission on our ward are psychiatric- and behavioural disorders. The relative high use of antipsychotics is in agreement with other studies although different prevalence rates for different samples of people were found [14-17].

Multiple drug use was associated with aggressive behaviour. There was also an association with attention seeking behaviour and involuntary measures, although not significant possibly due to small numbers. Many patients admitted to the ward have long histories of recurrent admissions to psychiatric hospitals and to specialised units of residential settings and it is likely that our findings indicate difficulties in the management of patients with socially disruptive behaviour. This is underlined by the finding that psychotropic drugs were used in high dosages and the tendency to prescribe multiple drugs in patients with a duration of stay of more than a year. The association between psychotic disorder and multiple medication was not surprising because this disorder is often accompanied with agitation. Therefore, combinations of antipsychotics with benzodiazepines and tranquillisers are frequently used. Another explanation for the association between psychotic disorder and multiple drug use is the fact that among patients with learning disabilities and aggressive behaviour sometimes an underlying psychotic disorder is suspected whereas with a formal psychiatric evaluation no psychotic symptoms are observed. The complex treatment of patients with socially disruptive behaviour is emphasised by the results of other studies among people with learning disabilities in which an association between such behaviour and the use of antipsychotic drugs was found [9, 18, 19]. The association between bizarre behaviour and multiple drug use may be explained by the fact that it is difficult to interpret this behaviour and that it may be related to severe disorders such as autistic disorder and psychotic disorder for which a broad spectrum of psychotropics are prescribed.

We did not consider the combined use of antipsychotics with anticholinergics as multiple psychotropic drug use as this combination is commonly used because of extrapyramidal adverse effects. Nevertheless, it is possible that many patients who were maintained on long-term antipsychotics, actually no longer require these agents, which may be a source of cognitive side-effects or

elevated mood in sensitive patients [20]. We found that four of nine multiple drug users who used anticonvulsants had no seizure disorder. Anticonvulsants are often used for psychiatric and behavioural purposes [21].

In this study, no effect of gender, age and level of intellectual functioning on multiple psychotropic drug use was found. The lack of a gender effect is consistent with most studies looking at this variable [8,13,16]. Concerning age and psychotropic use, some researchers found no relation whereas others have found that older people use more psychotropics [8,13,16]. Jacobson found that young and middle aged adults received higher rates of psychotropic medication than children, adolescents and older people [22]. Inconsistent results are reported concerning the association of level of intellectual functioning and psychotropic drug use [8,13,16].

In conclusion, we found a prevalence of multiple psychotropic drug use of 48% in this population. A clear association between multiple drugs and socially disruptive behaviour was found indicating that difficulties in the management of this behaviour is a common problem. More detailed investigations into the rationale of prescribing multiple drugs in settings for people with intellectual disabilities are needed.

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CHAPTER 5

General discussion

PSYCHOTROPIC DRUG USE: PRACTICE VERSUS EVIDENCE

A main finding of this thesis is the observation that physicians - in an effort to provide optimal care for their patients - 'struggle' with prescribing psychotropic drugs for many reasons. The variety of clinical settings that was studied in this thesis all comprised a highly complex patient population, with multiple psychiatric and somatic disorders. Another challenge for the prescribing physician is that present choice of available treatments may involve the use of drugs or procedures such as seclusion that have not been properly tried and tested. Randomised controlled trials (RCTs) of psychotropic drugs have provided little evidence for their efficacy and safety in study populations that are representative of those treated in actual clinical practice [1, 2]. Older patients, women of child bearing age or pregnant, and patients with mixed diagnoses and co-morbidity with (severe) personality disorders are excluded from most trials. Patients also often drop out because they experience adverse effects. Recently, Zimmerman et al [3] found that RCT patients only represent a minority of the patients with major depressive disorder treated in actual clinical practice: only 14% of those treated in daily practice would meet the inclusion criteria of a typical RCT on antidepressants. So, the results of studies on only a small fraction of patients with depressive disorder are generalised to all patients, assuming the effectiveness and safety are comparable.

The difficulties in conducting RCTs are also true for the populations we studied. Recent reviews on the use of antipsychotics in behavioural disorders and in schizophrenia in intellectually disabled adults concluded that there is a great lack of good quality trials conducted in this field [4, 5]. In addition, Cure and Carpenter [6] reviewed RCTs evaluating droperidol use in people with suspected acute psychotic illnesses and disturbed behaviour. The review was only able to include a few RCTs and concluded that the use of droperidol in this patient group is founded on clinical experience rather than on evidence from RCTs. In a systematic review of the use of sedative agents in intensive care settings, it was concluded that large RCTs studying the efficacy of different agents for short-term and long-term sedation are warranted [7]. There is insufficient evidence for the use of these drugs in intensive care settings. Evidence-based treatment is the paradigm of current medicine, while, especially in psychiatry, there are not enough valid data available, due to lack of

studies, poorly designed or executed studies, and, most frequently, the huge differences between patients studied in RCTs and those treated in daily practice.

UNDERTREATMENT VERSUS POLYPHARMACY

We have found two examples of suboptimal treatment in psychiatry: undertreatment of patients in need of pharmacotherapy; and possible overtreatment in the form of polypharmacy (the use of psychotropic drugs concomitantly).

This thesis presented studies on the prevalence of psychotropic drug use in a variety of clinical settings. We found that many patients with psychiatric or behavioural disorders appear to be undertreated with psychotropic drugs. In group homes, antidepressants or mood stabilisers, antipsychotics and anxiolytics were used infrequently in patients with affective, psychotic or anxiety symptoms. In psychiatric admission wards, a considerable number of patients with psychotic disorders did not use antipsychotics at the beginning of their hospitalisation, and consequently many were later secluded. Thus, undertreatment can lead to prolonged suffering and may result in more severe outcomes.

In two settings for the intellectually disabled, group homes and a specialised psychiatric ward, we observed a very high prevalence of concomitant use of psychotropic drugs. In studies conducted in other psychiatric settings, frequent polypharmacy was also observed [8]. Although, in many instances, the use of more than one psychotropic drug may be necessary and reasonable, irrational polypharmacy also frequently occurs [9]. In a recent publication, several circumstances that could lead to irrational use are mentioned [9]. The first circumstance concerns a patient doing poorly where the physician adds medication but is afraid to withdraw any of the other ineffective drugs. The second involves treatment of individual symptoms instead of relating symptoms primarily to the (main) diagnosis. Other circumstances may result from a failed cross-titration of two psychotropic drugs, inadequate dosing in cases of monotherapy, inadequate knowledge or lack of attention to pharmacodynamic or pharmacokinetic aspects of drugs, the wish to hasten a

therapeutic response and not well-studied recommendations of others. Some aspects play a role in the treatment of intellectually disabled people with psychiatric disorders. Polypharmacy may increase the risk of morbidity and mortality [9]. Possibly, untoward interactions and adverse effects are more prevalent in the population of intellectually disabled compared to the normal population [10, 11].

PSYCHOTROPIC DRUG USE VERSUS SECLUSION

Patients with severe disruptive or aggressive behaviour are common in mental health care [12]. Often, difficulties with pharmacotherapy occur in these patients due to poor compliance or other problems related to drug intake. The disruptive or aggressive behaviour itself may influence the choice of pharmacotherapy used in these patients [13]. We found that disruptive behaviour or aggression is an important factor associated with psychotropic drug use. It is likely that psychotropics prescribed in the 'struggle' of clinical practice are used not only to treat patients, but also to diminish danger for the patient or his environment. In group homes, socially disruptive behaviour was associated with antipsychotics and antidepressants. In a specialised ward for intellectually disabled adults, we found that a broad spectrum of drugs was used concomitantly to treat patients with socially disruptive behaviour.

Although many psychotropics, including antipsychotics, benzodiazepines, antidepressants, lithium and anticonvulsants, are used for their anti-aggressive properties, there is little evidence available for their effectiveness for this indication [14, 15]. Aggression is difficult to study because it is a heterogeneous phenomenon associated with many biological, psychological and social factors. As a consequence of the lack of evidence, most regulatory agencies have not approved psychotropics for the treatment of aggression [14, 15]. In contrast, several classical antipsychotics are registered in the Netherlands for the treatment of (psychotic) agitation during the 1960s and 1970s, during which time the requirements were less stringent [16].

Seclusion is applied to more than a quarter of newly admitted patients on psychiatric admission wards. It is likely that seclusion is considered less infringing than involuntary medication, but in the end, (forced) pharma-

cological treatment seems inevitable for a substantial proportion of secluded psychotic patients. As mentioned in Chapter 2.1, antipsychotic drugs are considered essential in both international and Dutch guidelines for the treatment of psychosis [17, 18]. So far, there has been no study evaluating the effectiveness of seclusion [19]. The choice of antipsychotics in aggressive patients with (psychotic) disorders can be considered more supported by valid data than the choice of seclusion. However, in addition to evidence, this choice also depends on other factors including restrictions of the Dutch law and the physicians' and patients' knowledge of and attitude towards psychotropics and seclusion.

CLASSICAL VERSUS ATYPICAL ANTIPSYCHOTICS

The 1998 Dutch guidelines for treatment of patients with psychotic disorders have not decided between classical or atypical antipsychotics for first-line treatment [18]. This debate on the choice of first-line treatment for psychosis is also still ongoing in literature [20-27].

We found that many psychotic patients initially use short-acting parenteral classical antipsychotics, mainly zuclopenthixol acetate. This is an interesting finding as there is no evidence that zuclopenthixol acetate is more effective than 'standard' care in controlling aggressive/disorganised behaviour or acute psychotic symptoms or in preventing adverse effects. Probably, it is more often used in urgent situations compared to other parenteral antipsychotics because of its 2-3 day action and low frequency of administration [28].

Regarding the choice of classical or atypical oral antipsychotics in newly admitted patients, severity of psychiatric illness was not found to be a determinant. However, if patients start with parenteral classical antipsychotics, they frequently continue oral treatment with the classical antipsychotics. The most likely reason is that short-acting parenteral antipsychotics are only available for the classical and not the atypical antipsychotic drugs. Therefore, it is likely that the coming availability of intramuscular atypical antipsychotics will rigorously change prescription patterns. Another factor that affects the choice of antipsychotics is (prior) occurrence of extrapyramidal syndromes. It

has been found that atypical antipsychotics tend to be selectively prescribed to patients with a history of extrapyramidal syndromes [29].

IMPLICATIONS OF THE STUDY

Research implications

RCTs into effects of psychotropic drugs in populations or indications that are difficult to study are warranted, even when such trials in themselves would not be enough to obtain formal approval for marketing. However, is this a realistic challenge? Conducting RCTs is extremely costly [30]. After registration for a specific indication, pharmaceutical companies may have only limited interest in conducting studies for other indications and in other populations. One reason for this is that the potential market size is often limited. Furthermore, the manufacturer can only be held liable for severe adverse effects that occur in patients with a registered indication, thus reducing the interest to register the drug for indications in high-risk patients [31].

Observational studies may play an important role in filling the gap between evidence based on RCTs and clinical practice. Because of lack of randomisation in observational studies, it is not possible to measure efficacy of psychotropic agents and, because of 'confounding by indication', the evaluation of effectiveness of one drug compared to another drug must be interpreted carefully. In addition to RCTs, however, well designed pharmacoepidemiological studies with the use of standardised measurements may contribute to evidence of psychiatric treatments especially in complex populations such as the population of intellectually disabled and for 'difficult indications' such as aggression. This may be even more important when studying treatments, such as using antipsychotics related to seclusion in RCTs, is impossible because of for example ethical reasons.

Databases may provide data to conduct these pharmacoepidemiological studies. In most existing databases, however, data of psychiatric admissions are lacking leading to missing of patients or to gaps of relevant data. It is therefore useful, in addition to these existing databases, to develop advanced databases containing data on psychotropic drug use and indications for this use, patient-

related and laboratory data with the collaboration of pharmacists, physicians and other professionals in psychiatric inpatient and outpatient settings.

The results of this thesis stress the need for research on the effectiveness and the adverse effects of seclusion. The finding that (forced) antipsychotic treatment early during hospitalisation will probably prevent patients from being secluded should be confirmed in other studies. It is also important to discern whether our findings on the association between antipsychotics and seclusion are typical for the Dutch mental health care system. We recommend that studies on the association between the use of psychotropics and seclusion are conducted on admission wards with different cultures of clinical practice.

Patients who are admitted to acute admission wards often have a history of outpatient psychotropic drug use. Therefore, future studies on determinants for the choice of atypical or classical antipsychotics should also consider the psychotropic drug use prior to the psychiatric admission. In addition, history of extrapyramidal syndromes should be evaluated in the context of appropriate choice of antipsychotics.

Clinical implications

Evidence for prescribing (multiple) psychotropics for aggression is scarce and experimental treatments should be evaluated using a wide range of observational methods to provide more comprehensive and objective ratings of patients' progress in clinical practice [9].

If there are good reasons to use forced medication, it is possible to do so within the limits of the Dutch law. In avoiding seclusion (a non-evidence based intervention), psychiatrists should apply forced medication more frequently. Against the background of the discussion in the Netherlands on involuntary treatment [32], the results of this study also support a modification of the Dutch law 'Compulsory admission into psychiatric hospitals' (BOPZ act) with involuntary treatment applied more easily.

A diversity of factors may be responsible for undertreatment in residents with psychiatric or behaviour disorders living in group homes as mentioned in

Chapter 4.1. It is likely that better recognition of (atypical) symptoms and easier access to psychiatric services may prevent intellectually disabled residents from some unnecessary suffering. Finally, pharmaco-epidemiological research of psychotropic drug use teaches us more about clinical practice in which physicians and patients struggle for optimal treatment.

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Chapter 6

Summary

INTRODUCTION

The prescribing of psychotropic drugs in clinical practice is influenced by a variety of factors, including the indications for treatment (both registered and off-label) and reflecting changes in guidelines and attitudes in psychiatry with its current emphasis on biological aspects and evidence-based mental health care. Epidemiological factors such as the prevalence of psychiatric disorders and cultural values such as the role of individual autonomy in our Western world also play a role. The physician, in collaboration with the patient, has to make choices on (psychopharmacologic) treatment. Choosing a treatment is often difficult especially for severely ill patients with psychiatric and somatic co-morbidity as these patients are routinely excluded from randomised controlled trials (RCTs) resulting in limited evidence for drug efficacy in this patient group. Studies on the determinants of psychotropic drug use may help to explore the 'gap' between evidence and clinical practice.

The main objectives of this thesis were to establish the prevalence of psychotropic drug use as well as possible determinants associated with its use in multiple clinical settings: psychiatric admission wards, an intensive care unit and two settings for the intellectually disabled.

PSYCHOTROPIC DRUG USE IN PSYCHIATRIC ADMISSION WARDS

Antipsychotic drugs are essential in the treatment of patients suffering from psychotic disorders. The introduction of atypical antipsychotics has changed treatment options dramatically. Although the newer agents seem to be superior with regard to the lower risk of extrapyramidal symptoms, they have been associated with other side effects such as weight gain.

In Chapter 2.1, we evaluated the question which class of antipsychotics (classical versus atypical) is prescribed preferentially in newly admitted patients on psychiatric wards and the determinants affecting this decision. In a retrospective cohort design, using the drug database and clinical database of the participating hospitals, linked anonymously through record linkage methodology, patients were followed from date of admission until discharge from hospital during 1997-1999. We found that the most frequently prescribed

oral antipsychotic drugs were classical agents: zuclopenthixol (33.7%), pimozide (13.4%) and haloperidol (12.6%). The proportion of atypical agents used was 27.8%, consisting of clozapine (1.9%), olanzapine (14.8%) and risperidone (11.1%). No statistically significant difference was found between patients with varying severity of disease, as indicated by GAF-score and type of ward (open versus closed). Initial choice for short-acting parenteral classical antipsychotics was significantly associated with follow-up prescriptions of oral classical antipsychotics. Therefore, we predict that upcoming introductions of short-acting parenteral formulations of atypical agents are likely to have a large impact on the subsequent oral antipsychotic treatment.

Seclusion is one of the strategies to cope with disruptive and violent behaviour in psychiatric patients. No studies on the effectiveness of seclusion are available and the relationship between psychotropics and the application of seclusion has hardly been studied.

In Chapter 2.2, we looked at the temporal relationship between the use of antipsychotics and seclusion. Again, data extracted from a patient database linked to the hospital pharmacy database were retrospectively collected over the years 1997-1999. The study population consisted of 996 newly and consecutively admitted patients of 16 years or older with a complete first hospitalisation record of four days or longer on one of the participating admission wards. A high prevalence of seclusion was found: over a quarter (28.6%) of the patients was secluded at least once during their hospitalisation. This statistic may be related to the Dutch situation where involuntary hospitalisation does not mean that the patient has to accept the proposed medical treatment. Young age, a low GAF (Global Assessment of Functioning) score indicating major impairment in functioning, involuntary hospitalisation and a diagnosis of bipolar disorder (manic episode) were all factors significantly associated with seclusion. In contrast with other studies, a diagnosis of psychotic disorder was not associated with seclusion. It was found that antipsychotic treatment in patients with psychotic disorders was significantly associated with a delay of seclusion with an adjusted hazard ratio of 0.6 (95% confidence interval: 0.3-1.0) and, although not statistically significant, with a lower risk of seclusion with a relative risk of 0.7 (95% confidence interval: 0.5-

1.2). Furthermore, in a substantial proportion of the patients, antipsychotic therapy was only initiated during or directly following seclusion with a relative risk of 2.0 (95% confidence interval: 1.2-3.4). This suggests that, in patients with psychotic disorders, not using antipsychotics is associated with aggression or violence for which seclusion is needed. Pharmacological treatment seems inevitable for a substantial proportion of secluded psychotic patients and its earlier use might have prevented patients from being secluded.

PSYCHOTROPIC DRUG USE IN A GENERAL INTENSIVE CARE UNIT

Although psychiatric disorders frequently occur in intensive care settings and psychotropic drugs are often used, little is known about the determinants associated with psychotropic drug use in an intensive care unit. The fluctuating course of critical illness complicates the assessment of individual needs for psychotropic drugs along with highly variable patterns of drug metabolism and elimination.

In Chapter 3.1, we studied determinants of psychotropic drug use in a general intensive care unit (ICU). We retrospectively collected data for the first three months of 1995 from a consecutive sample of 137 patients aged 18 years or older. To deal with varying lengths of hospitalisation, 'bed-days' were taken as unit of analysis. The odds ratios for the use of benzodiazepines, antipsychotics or both were calculated comparing exposed days with unexposed days for gender, age, length of stay, reason for admission and disease severity indicated by APACHE (Acute Physiologic and Chronic Health Evaluation)-II scores. The prevalence of psychotropic drug use was 42.3%. Benzodiazepines were used in 35.8% of the patients, frequently at a high dosage (average dosage of 9.9 DDDs per day). Antipsychotics were prescribed in 17.5% of all patients, typically in low dosages with an average dosage of 0.5 DDDs per day. The association of high APACHE-II scores, a long ICU stay and an admission for non-surgical reasons with psychotropic drug use may be an indication that severely ill patients are likely to suffer from a delirium. An alternative explanation is that combined use of benzodiazepines and antipsychotics may prolong the stay in the ICU because of excessive sedation with cognitive impairment.

In this study, patients who used psychotropic drugs (cases) acted as their own controls because periods of drug exposure were compared to those of non-exposure. In this analysis, no corrections were made with the fact that observations were correlated.

In Chapter 3.2, we compared this design with a logistical binomial model to adjust for correlated measures, or cluster effects through repeated measures. We found that, although adjustment did not result in major changes in the odds ratios found, adjustment has greater effect with more observations per cluster.

PSYCHOTROPIC DRUG USE IN SETTINGS FOR PEOPLE WITH INTELLECTUAL DISABILITIES

In previous studies, prevalence of psychotropic and/or anticonvulsant drug use in intellectually disabled persons was high, ranging from 44-60% in institutions and 35-45% in community settings. Recurrent crises because of aggressive and other disruptive behaviour are strongly associated with psychotropic drug use and pharmacotherapy attempts with multiple drugs. We conducted two studies on the use of psychotropic drugs among intellectually disabled patients.

In Chapter 4.1, the point prevalence of psychotropic drug use in a problem behaviour group (PBG) of intellectually disabled group home residents was compared to a random group (RG) of residents and possible determinants of group membership were studied. From all group homes in The Netherlands, 573 problematic residents were selected by staff (one resident from each home) and 1479 residents were randomly sampled from all the homes. Mental disorders were measured with Dutch versions of the Reiss Screen for Maladaptive behavior and the Psychopathology Instrument for Mentally Retarded Adults. We found that, as expected, psychotropic drug use was much higher in residents of the group homes with behavioural problems compared to a random group of residents. Psychotropics, excluding anticonvulsants, were used by 52.6% of the problem behaviour group and by 22.8% of the random group. In the PBG, 17.3% used three or more concomitantly prescribed drugs and in the RG, 7.3%. Three or more categories of psychotropic drugs were used concomitantly by 11.1% of the PBG and 2.8% of the RG. A high prevalence of

antipsychotics (41.2% in the PBG; 16.7% in the RG), often prescribed at low dosages and for a broad spectrum of indications, was found. Low dosages of these agents were prescribed probably because beneficial effects of low dosages of these agents have been reported in intellectually disabled people with behavioural problems. It was found that young age, psychotic, anxiety and aggression symptoms were significantly associated with the PBG. It is likely that staff finds it difficult to deal with this group of residents, which would be in agreement with other studies. Remarkably, a low prevalence of antidepressants, mood stabilisers, antipsychotics and anxiolytics in patients with the corresponding symptoms was found. This suggests that a considerable number of residents remain undertreated.

In Chapter 4.2, we examined the prevalence and possible determinants of multiple psychotropic drug use in patients with mild intellectual disabilities or borderline intellectual functioning and psychiatric or behavioural disorders admitted to a specialised closed ward for prolonged treatment and rehabilitation. Data on psychotropics and possible determinants of use were retrospectively collected for the years 1992-1997 from a consecutive sample of 96 patients of 16 years or older concerning their first admission of at least one month. Multiple drug use was defined as concomitant use of a combination of benzodiazepines / tranquillisers / antipsychotics / anticonvulsants / antidepressants. We found that the point prevalence of psychotropic drugs at admission was 63.5%, the period prevalence during hospitalisation was 79.2% and the point prevalence at discharge was 69.7%. Of all psychotropics, use of antipsychotics during admission (66.7%) was highest as seen in previous studies. Multiple drug use was found in half of the patients. Psychotropics were used in high dosages and there was a tendency to prescribe multiple drugs for patients with duration of stay longer than a year. Furthermore, psychotic disorder, aggressive, bizarre, attention seeking behaviour and involuntary measures were associated with multiple psychotropic drug use. Many patients have long histories of recurrent admissions to psychiatric hospitals and specialised units of residential settings. It is likely that our findings, especially the association with aggressive and attention seeking behaviour, indicate difficulties in the management of patients with socially disruptive behaviour. This is emphasised by the association of multiple drug use with psychotic

disorder and is in line with other studies that found an association between such behaviour and the use of antipsychotics.

In conclusion, we investigated patterns of psychotropic drug use and identified possible determinants for their use in a variety of clinical settings. In these settings, physicians deal with complex patients for whom the evidence of the effectiveness and safety of available treatments is scarce. The studies show that observational pharmacoepidemiological studies may play an important role in analysing the gap between the evidence derived from non-representative RCTs and the complex patients in routine clinical practice.

Chapter 7

Samenvatting

INLEIDING

Allerlei factoren hebben invloed op het voorschrijven van psychofarmaca in de klinische praktijk zoals geregistreerde en off-label indicaties van geneesmiddelen, de veranderende opvattingen over psychiatrische stoornissen, de huidige nadruk op biologische psychiatrie en 'evidence based' geestelijke gezondheidszorg. Daarnaast spelen epidemiologische factoren, met name de prevalentie van psychiatrische stoornissen, en culturele waarden zoals de nadruk op individuele autonomie in onze Westerse wereld een rol. In deze complexe situatie is het de arts die, in overleg met de patiënt, keuzes moet maken in de (psychofarmacologische) behandeling. Dit is met name moeilijk bij ernstige zieke psychiatrische patiënten met psychiatrische en somatische comorbiditeit. Over de farmacologische behandeling van dergelijke patiënten is relatief weinig bekend omdat zij meestal uitgesloten worden van gerandomiseerd klinisch onderzoek (randomised controlled trial: RCT). Hierdoor is er weinig bewijs voor de werkzaamheid van geneesmiddelen in deze patiëntengroep ondanks dat psychofarmaca in de dagelijkse klinische praktijk veel worden voorgeschreven. Observationeel farmaco-epidemiologisch onderzoek naar determinanten van het gebruik van psychofarmaca kan behulpzaam zijn in het verkennen van de kloof tussen wetenschappelijk bewijs en deze praktijk.

In dit proefschrift worden diverse onderzoeken beschreven naar de prevalentie van psychofarmacagebruik en naar mogelijke determinanten die van invloed zijn op het gebruik in verschillende klinische populaties: op psychiatrische opnameafdelingen, een intensive care unit en twee voorzieningen voor mensen met een verstandelijke handicap.

PSYCHOFARMACAGEBRUIK OP PSYCHIATRISCHE OPNAMEAFDELINGEN

Antipsychotica zijn onontbeerlijk in de behandeling van patiënten die lijden aan psychotische stoornissen. Door de introductie van atypische antipsychotica zijn de behandelingsmogelijkheden aanzienlijk uitgebreid. Hoewel de nieuwere middelen voordelen lijken te hebben wat betreft de kans op extrapiramidale symptomen, kunnen ze wel andere bijwerkingen zoals gewichtstoename tot gevolg hebben.

In Hoofdstuk 2.1 wordt een onderzoek beschreven naar welk type antipsychoticum (klassiek versus atypisch) bij voorkeur wordt voorgeschreven aan nieuw opgenomen patiënten op psychiatrische opnameafdelingen en welke factoren deze keuze beïnvloeden. In een retrospectief cohort onderzoek werden patiënten die gedurende de jaren 1997-1999 voor de eerste maal opgenomen werden van opname tot ontslag gevolgd. Hierbij werd gebruik gemaakt van de geneesmiddelendatabase van de deelnemende ziekenhuizen die anoniem gekoppeld werd aan de patiëntendatabase. De meest voorgeschreven orale antipsychotica waren klassieke middelen: zuclopenthixol (33,7%), pimozide (13,4%) en haloperidol (12,6%). Ruim een kwart (27,8%) van de 522 nieuw opgenomen patiënten die met een antipsychoticum behandeld werd, gebruikte in eerste instantie een atypisch middel waarbij olanzapine door 14,8% van de patiënten, risperidon door 11,1% en clozapine door 1,9% werd gebruikt. Ernst van de ziekte zoals gemeten door de GAF (Global Assessment of Functioning) score en type opnameafdeling (open of gesloten) was niet van invloed op de keuze tussen klassieke of atypische middelen. Het bleek dat wanneer in eerste instantie voor kortwerkende klassieke parenterale antipsychotica gekozen wordt, daarna vaak klassieke orale antipsychotica worden voorgeschreven. De op handen zijnde introductie van kortwerkende parenterale atypische antipsychotica zal daarom naar alle waarschijnlijkheid de keuze van het orale antipsychoticum dat vervolgens wordt voorgeschreven (klassiek of atypisch) sterk beïnvloeden.

Separatie is een van de maatregelen die genomen kan worden om ontwrichtend en agressief gedrag van psychiatrische patiënten te hanteren. Er is geen onderzoek bekend naar de werkzaamheid van separatie. Het verband tussen het voorschrijven van antipsychotica en separatie is eveneens nauwelijks onderzocht.

In Hoofdstuk 2.2 wordt een onderzoek beschreven naar de relatie tussen het voorschrijven van antipsychotica en separatie. Opnieuw werden gegevens van de patiënten database gekoppeld aan de apotheek database retrospectief verzameld van 1997-1999. De onderzoekspopulatie bestond uit 996 achtereenvolgens opgenomen patiënten van 16 jaar en ouder die voor de eerste maal vier of meer dagen opgenomen waren op een opnameafdeling.

Separatie werd vaak toegepast: meer dan een kwart (28,6%) van de patiënten werd tenminste een keer gesepareerd tijdens de opname. Dit heeft waarschijnlijk deels te maken met de Nederlandse situatie: een onvrijwillige opname betekent niet dat een patiënt gedwongen kan worden tot een (medicamenteuze) behandeling. Een jonge leeftijd, een lage GAF score wijzend op een laag niveau van functioneren, onvrijwillige opname en een bipolaire stoornis (manische episode) waren significant geassocieerd met separatie. In tegenstelling tot diverse andere onderzoeken bleek er geen relatie tussen de diagnose psychotische stoornis en het toepassen van separatie te zijn. Anti-psychotische behandeling was significant geassocieerd met een latere toepassing van separatie met een gecorrigeerde hazard ratio van 0,6 (95% betrouwbaarheidsinterval: 0,3-1,0) en, hoewel niet significant, met een lager risico op separatie met een relatief risico van 0,7 (95% betrouwbaarheidsinterval: 0,5-1,2). Bovendien bleek dat in een aanzienlijk deel van de patiënten met antipsychotica begonnen wordt tijdens of kort na separatie met een relatief risico van 2,0 (95% betrouwbaarheidsinterval: 1,2-3,4). Waarschijnlijk is agressie of geweld geassocieerd met psychotische patiënten die geen antipsychotica gebruiken waarbij vervolgens separatie wordt toegepast. Een behandeling met antipsychotica lijkt onvermijdelijk voor een aanzienlijk deel van de psychotische patiënten en mogelijk kan het gebruik van deze middelen aan het begin van de opname separatie voorkomen.

PSYCHOFARMACAGEBRUIK OP EEN ALGEMENE INTENSIVE CARE AFDELING

Hoewel psychiatrische aandoeningen vaak voorkomen op intensive care afdelingen en psychofarmaca frequent gebruikt worden, is er weinig bekend over de factoren die het gebruik van deze middelen op deze afdelingen beïnvloeden. Het vaak stormachtige beloop van de ernstige aandoeningen, het sterk wisselende metabolisme en de wisselende uitscheiding van geneesmiddelen bemoeilijken de beoordeling van de individuele behoefte aan psychofarmaca.

In Hoofdstuk 3.1 wordt een onderzoek beschreven naar determinanten van psychofarmacagebruik op een algemene intensive care afdeling. Retrospectief werden gegevens verzameld over de eerste drie maanden van 1995 van 137 patiënten van 18 jaar en ouder. Omdat de duur van de opname van de

patiënten nogal uiteenliep, werden 'bed-dagen' als analyse eenheid gebruikt. De odds ratios van het gebruik van benzodiazepines, antipsychotica of beiden werden berekend waarbij de dagen waarop psychofarmaca werden gebruikt vergeleken werden met dagen waarop deze middelen niet werden gebruikt voor geslacht, leeftijd, opnameduur, reden voor opname en ernst van de aandoening aangeduid door APACHE ('Acute Physiologic and Chronic Health Evaluation')-II scores. De prevalentie van psychofarmacagebruik was 42,3%. Benzodiazepines werden door 35,8% van de patiënten in hoge doseringen (gemiddeld 9,9 DDDs per dag) gebruikt. Antipsychotica werden voorgeschreven aan 17,5% van de patiënten in lage doseringen van gemiddeld 0,5 DDDs per dag. Het gebruik van psychofarmaca was geassocieerd met een hoge APACHE-II score, een langdurige opname en een opname voor niet chirurgische redenen. Het is aannemelijk dat deze ernstig zieke patiënten een groot risico lopen op een delier. Daarnaast is het mogelijk dat gecombineerd gebruik van benzodiazepines en antipsychotica het verblijf op de intensive care verlengd vanwege overmatige sedatie met verslechtering van de cognitieve functies.

In het bovengenoemde onderzoek fungeerden patiënten die psychofarmaca gebruikten (cases) als hun eigen controles omdat dagen waarop patiënten psychofarmaca gebruikten, werden vergeleken met dagen waarop geen psychofarmaca werden gebruikt.

Aanvullend op dit onderzoek wordt in Hoofdstuk 3.2 bovengenoemde onderzoeksozopzet vergeleken met een andere opzet: een logistisch-binomiaal model om te corrigeren voor gecorreleerde waarnemingen of cluster effecten door herhaalde metingen. Aangetoond wordt dat hoewel correctie niet leidde tot grote veranderingen in de odds ratios, correctie van grotere invloed was naar mate er meer observaties per cluster plaatsvonden.

PSYCHOFARMACAGEBRUIK IN VOORZIENINGEN VOOR VERSTANDELIJK GEHANDICAPTEN

Uit eerdere onderzoeken bij verstandelijk gehandicapten is gebleken dat de prevalentie van psychofarmaca en/of anti-epileptica gebruik hoog is met een spreiding van 44-60% in intramurale woonvoorzieningen en van 35-45% in meer maatschappelijk geïntegreerde voorzieningen. Terugkerende crisis-

situaties vanwege agressief of ander ontwrichtend gedrag zijn in sterke mate geassocieerd met het gebruik van psychofarmaca en polyfarmacie komt veel voor.

In Hoofdstuk 4.1 en 4.2 worden twee onderzoeken beschreven naar het gebruik van psychofarmaca door mensen met een verstandelijke handicap.

In Hoofdstuk 4.1 werd de punt prevalentie van het gebruik van psychofarmaca bij verstandelijk gehandicapte bewoners van gezinsvervangende tehuizen met gedragsproblemen vergeleken met een aselechte groep van bewoners. Factoren die mogelijk samenhangen met een van beide populaties werden bestudeerd. Uit alle gezinsvervangende tehuizen in ons land werden 573 bewoners met probleemgedrag door de staf geselecteerd en 1479 bewoners werden aselekt gekozen. Psychiatrische stoornissen werden gemeten met Nederlandse versies van de 'Reiss Screen for maladaptive behavior' en de 'Psychopathology Instrument for Mentally Retarded Adults'. Zoals verwacht, bleek de groep van bewoners van gezinsvervangende tehuizen met gedragsproblemen veel meer psychofarmaca te gebruiken dan de aselekt gekozen groep bewoners. Psychofarmaca exclusief anti-epileptica werden door 52,6% van de probleemgroep gebruikt en door 22,8% van de aselekt gekozen groep bewoners. In de probleemgroep gebruikte 17,3% drie of meer psychofarmaca tegelijkertijd en in de aselechte groep 7,3%. Door 11,1% van de probleemgroep en 2,8% van de aselechte groep werden psychofarmaca uit drie of meer verschillende categorieën gelijktijdig gebruikt. De prevalentie van anti-psychotica, vaak voorgeschreven in lage doseringen en voor uiteenlopende indicaties, was hoog (41,2% in de probleemgroep; 16,7% in de aselechte groep). Lage doseringen van deze middelen werden waarschijnlijk voorgeschreven omdat hiervan gunstige effecten bij verstandelijk gehandicapten met gedragsproblemen worden beschreven. De groep van bewoners met probleemgedrag was significant jonger. Psychotische symptomen, symptomen van angststoornissen en agressieve gedragingen kwamen in deze groep significant vaker voor. Waarschijnlijk vinden groepsleiders het moeilijk deze bewoners te begeleiden wat in overeenstemming is met de bevindingen van andere onderzoeken. Het is opvallend dat er weinig antidepressiva, stemmingsstabilisatoren, antipsychotica en anxiolytica werden voorgeschreven in

bewoners met de corresponderende symptomen. Waarschijnlijk wordt een aanzienlijk deel van de bewoners onderbehandeld.

In Hoofdstuk 4.2 wordt een onderzoek beschreven naar de prevalentie en mogelijke determinanten van polyfarmacie bij patiënten met een lichte verstandelijke handicap of zwakbegaafdheid en psychiatrische of gedragsstoornissen. Deze patiënten zijn opgenomen op een gespecialiseerde gesloten afdeling voor langdurige behandeling en rehabilitatie. Gegevens over psychofarmaca en factoren die daar mogelijk mee samenhangen werden retrospectief verzameld in een groep van 96 patiënten van 16 jaar en ouder die minstens een maand opgenomen waren tussen 1992-1997. Polyfarmacie werd gedefinieerd als het gelijktijdig gebruik van benzodiazepines/tranquillisers/antipsychotica/anti-epileptica/antidepressiva. Er werd een punt prevalentie van psychofarmaca gebruik bij opname gevonden van 63,5%, een periode prevalentie gedurende de opname van 79,2% en een punt prevalentie bij ontslag van 69,7%. Van alle psychofarmaca werden antipsychotica tijdens opname het meest gebruikt (66,7%), zoals dat ook in eerdere onderzoeken is gevonden. Polyfarmacie kwam bij de helft van de patiënten voor. Psychofarmaca werden in hoge doseringen gebruikt. Er was een tendens om meerdere middelen tegelijkertijd voor te schrijven aan patiënten met een opnameduur van meer dan een jaar. Daarnaast waren psychotische stoornis, agressief, bizar, aandachtvragend gedrag en vrijheidsbeperkende maatregelen geassocieerd met polyfarmacie. Veel patiënten hebben een uitgebreide voorgeschiedenis van opnames in psychiatrische ziekenhuizen en gespecialiseerde afdelingen van voorzieningen voor verstandelijk gehandicapten. De gevonden associatie met agressief en aandachtvragend gedrag wijst waarschijnlijk op moeilijkheden in de begeleiding van patiënten met sociaal ontwrichtend gedrag. Dit wordt benadrukt door de associatie van polyfarmacie met psychotische stoornissen en komt overeen met andere onderzoeken waarin een associatie wordt gevonden tussen zulk gedrag en antipsychotica gebruik.

Samenvattend zijn patronen van psychofarmacagebruik onderzocht en zijn mogelijke determinanten van het voorschrijven van deze middelen in verschillende klinische populaties in kaart gebracht. In deze populaties gaat het

om patiënten die zich in complexe situaties bevinden waarbij wetenschappelijke onderbouwing van effectiviteit en veiligheid van psychofarmaca schaars is. De onderzoeken laten zien dat observationeel farmaco-epidemiologisch onderzoek een belangrijke rol kan spelen om de kloof tussen wetenschappelijke bewijs gebaseerd op niet representatieve RCTs en de klinische praktijk te analyseren.

LIST OF PUBLICATIONS

Articles marked with an asterix (*) relate to work described in this thesis.

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CURRICULUM VITAE

Joost Jan Stolker was born in Amstelveen, the Netherlands, on February 20th, 1965. Following completion of his secondary education at the 'Christelijke Scholengemeenschap Buitenveldert' (gymnasium β) in 1983, he chose to study Medicine at the Free University in Amsterdam. He was awarded his MD in 1991. He then worked at a specialised psychiatric admission ward for the elderly at the 'Provinciaal Ziekenhuis Santpoort' (Supervisor: D. Stam) and the 'Centrale Riagg Dienst' in Amsterdam (Supervisor: R.A. Achilles). After studying outcome-indicators of chronic psychiatry (Supervisor: Prof. dr F.G. Zitman) at the Department of Psychiatry, University Hospital Nijmegen, during 1992-1993, he specialised in psychiatry at the same hospital (Supervisor: Prof. dr F.A.M. Kortmann). He continued his training at a specialised psychiatric clinic for the intellectually disabled, a branch of Altrecht Institute for Mental Health Care. Since September 1997, he has been practising as a psychiatrist at this specialised clinic. He also then started his PhD project at the Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University.