The Use of Neuroleptics

SBU Summary and Conclusions

INTRODUCTION

Neuroleptics is a general term for a wide range of drugs used to treat severe mental illness, mainly psychotic disorders.

Delusions and hallucinations are characteristic symptoms of psychoses. Patients may, for example, hear voices which they feel persecute or control them. Some patients with prolonged psychoses frequently experience disturbances in thought patterns and dulled emotions. People affected tend to avoid social contact.

Treatment of psychotic conditions aims among other things at alleviating acute agitation and anxiety, reducing psychotic symptoms, and preventing recurrence of the disease. Neuroleptics play an important role in this aspect of treatment.

The mental health services first used neuroleptics during the 1950s. Previously, no forms of treatment had been particularly effective in treating severe mental illness. Treatments available at that time included electroconvulsive (electric shock) therapy and insulin coma therapy. Untreated, severe psychiatric disorders cause aggressiveness and violence in some people, and patients may present substantial risks both to themselves and others. Consequently, many psychotic patients at that time were isolated in tightly guarded hospital departments with locked doors and barred windows.

When neuroleptics were introduced, their effects were dramatic, immediate, and obvious. The drugs had, for instance, the capacity to calm acute, chaotic conditions and ameliorate psychotic symptoms. Consequently, neuroleptics rapidly came into wide-spread use in psychiatric care, and the situation for psychotic patients changed radically. Certain treatment methods, such as strait-jackets and isolation cells, were phased out, and patients could move about more freely. Large groups of patients were offered training in social skills, and with the help of neuroleptic therapy they could be discharged from mental hospitals for rehabilitation as outpatients.

Initial enthusiasm over the effects of neuroleptic therapy led to the generous prescription of these agents for ever widening indications and an increasing number of patient groups.

Neuroleptic therapy was eventually subjected to criticism by patient groups and the research community. This criticism was directed at the side effects of neuroleptic therapy, which in some patients were severe and permanent.

Research on neuroleptics during the past decades has aimed largely at identifying active mechanisms and side effects. Attempts are being made to achieve greater precision in neuroleptics to reduce side effects and develop methods to establish appropriate doses.

A wide range of neuroleptics have been marketed since the 1950s, 15 of which are now used in Sweden.

Given the background information presented above, the Swedish government charged SBU with reviewing the scientific literature on neuroleptic therapy.

A project group at SBU systematically and critically analyzed more than 2000 published manuscripts in this field. The manuscripts were selected based on their scientific quality, ie only studies that fulfilled certain criteria for acceptable scientific standards were included in the review. In areas where the strict criteria could not be met, other studies were also analyzed. Each chapter in this report specifies the grounds for, and limitations in, selecting the scientific literature. The following report is based entirely on information from the scientific literature.

Active mechanisms of neuroleptics and effects in treatment of psychoses

Soon after neuroleptics were introduced for treating mental disorders in the 1950s, several studies confirmed that these medications had more than dulling and tiring effects. An antipsychotic effect was also confirmed, in that neuroleptic therapy reduced hallucinations, delusions, and thought disorders.

Research has also shown that the antipsychotic effects of neuroleptics can be achieved at substantially lower doses than has been previously believed. Furthermore, greater knowledge has been gained about the limited or negligible benefits of neuroleptics in treating diseases other than psychoses. It has also been established that not all patients with psychotic disorders improve with neuroleptic therapy.

Neuroleptics work by blocking signals between nerve cells in the brain that control thought, emotions, mobility, and coordination. The processes that cause patients' symptoms to decline or disappear are not fully understood. The clinical effects of neuroleptics are, however, well documented in the scientific literature.

Fifty-five well-controlled, prospective studies concerning the effects of neuroleptics on psychotic symptoms were thoroughly reviewed. These studies show that neuroleptic therapy achieves significantly better results than placebo (biologically inactive treatment) in patients with schizophrenia. Documentation concerning the effects on other psychotic disorders is, however, lacking. The improvements that can be achieved by neuroleptics in treating schizophrenia apply to both the acute phase and continuing treatment.

The reviewed studies also show that when the onset of psychosis is rapid, patients often improve spontaneously. Hence, when possible, it is advisable to wait a few weeks before initiating neuroleptic therapy. Neuroleptics are often less beneficial in patients who have gone untreated for several years. The studies offer no scientific evidence that high-dose treatment is generally superior to moderate doses. Several studies suggest that dose levels below those used in current practice may be adequate if care environments and psychological services are appropriately designed.

Although neuroleptics have been used for 40 years, none of the studies offer any reliable predictions of the long-term prognosis following neuroleptic therapy. Some research indicates that neuroleptic therapy favorably affects the prognosis for the first 5 years, and that early treatment, particularly in combination with other interventions, improves the long-term treatment results. Neuroleptics do not relieve symptoms in nearly one third of the patients with prolonged psychosis, and have an insufficient effect in another third. Of the patients who are successfully treated with neuroleptics, a large percentage relapse within 2 years after discontinuing treatment. Other patients may discontinue neuroleptic therapy without experiencing further psychotic symptoms, including approximately 10% of those with schizophrenia. No methods currently exist to identify this group in advance.

In summary, the literature shows that neuroleptic therapy is superior to other known treatment for patients with schizophrenia. In some patients, further improvement can be achieved when neuroleptics are used in combination with other interventions.

Neuroleptics combined with other therapy for psychosis

Regarding continued treatment following the acute phase of schizophrenia, several well-controlled studies show that community-based rehabilitation combining neuroleptic therapy with psychosocial interventions (family intervention and family support, social skills training, individual therapy, group therapy) may yield better results in many patients than neuroleptic therapy alone. One study shows that a combined approach reduces the need for neuroleptics, resulting in fewer side effects. Since fewer patients relapse, combined treatment may be more cost effective than traditional treatment for psychosis. Hence, care needs are less demanding, and more patients can function socially and join the work force. Despite these positive results, major problems remain concerning the rehabilitation of patients with schizophrenia. These problems are due, in part, to persistent symptoms such as withdrawal, lack of initiative, and lower emotional capacity.

Neuroleptics cannot be replaced by psychosocial treatment, but data suggest that low-dose therapy may be adequate, particularly in cases of acute psychosis, if patients are made to feel secure and understood.

Excessive use of neuroleptics

Naturally it is important to try to reduce the side effects from neuroleptic therapy, initially by confining the indications for treatment to the groups of patients who may actually benefit from these drugs. The view on neuroleptic therapy has become more critical and conservative, and in recent years the use of neuroleptics has declined somewhat in Sweden.

Nevertheless, it appears that neuroleptics continue to be overprescribed. Pharmaceutical statistics show that approximately 30% of neuroleptics are given to patients in whom the side effects of treatment may outweigh the benefits.

Treatment of the elderly

Brain processes change as people age. In most people, transmittor substances (mainly noradrenaline and dopamine) acting between the various nerve cells in the brain begin to decline around the age of 65 years. This process also influences how people react to certain drugs. How older people react to drugs and their side effects differs from how younger people react.

The scientific literature does not support the use of neuroleptic therapy in elderly people, except for those with psychotic symptoms. Current evidence suggests a restrictive approach toward neuroleptics in elderly patients, mainly because elderly people are more susceptible to side effects from neuroleptics, but also because the effects of neuroleptics are enhanced by interactions with other drugs, and because drugs remain active longer in the elderly.

Several studies have shown that neuroleptics are not superior to placebo in treating dementia. The side effects, however, may be substantial, although no studies have satisfactorily shown this in patients receiving neuroleptic therapy for dementia. Similarly, there have been no studies comparing the effects of medications with the effects of enhanced nursing intervention in dementia patients.

A study of elderly patients in nursing homes estimates that approximately 30% are being treated with neuroleptics, and that 6% of all persons above 75 years of age receive neuroleptic therapy. The indications underlying this relatively large percentage are unknown, but since dementia is the most common psychiatric diagnosis in these age groups, it would appear that neuroleptics are greatly over-prescribed for elderly patients in Sweden.

In elderly patients, neuroleptics should be prescribed only for those with psychotic disorders, and then at doses substantially below the levels prescribed for young and middle-aged patients.

Treatment of children and adolescents

Few studies address the treatment of children and adolescents, and none analyze potential differences in treatment effects between boys and girls. Studies report serious side effects of neuroleptic therapy in about 30% of patients below 18 years of age.

Considering the scant scientific evidence, neuroleptic therapy should be restricted to children and adolescents with severe psychoses, serious behavioral disorders related to autism, and severe tics related to Tourette's syndrome.

Treatment of the mentally retarded

The scientific literature offers little or no support for neuroleptic therapy in the young mentally retarded, not even in patients with self-destructive behavior. Some research supports low-dose treatment in mentally retarded adults, if no other treatment can be found to improve disabling, disruptive behavior.

Treatment of substance abusers

The literature shows that neuroleptics are not superior to placebo in treating acute abstinence and delirium tremens in substance abusers. Similarly, neuroleptics should not be used in treatment for heroin detoxification, where the side effects are more severe, and the treatment effects are inferior to placebo.

Neuroleptics are more effective than placebo in treating persistent agitation, despondency, and irritability after the acute phase of abstinence. The same may apply to alcohol craving. However, the risks for neurological side effects from neuroleptics are greater in abusers than in people with no substance abuse problems. These medications should therefore be avoided.

Treatment of sleep disorders, anxiety, depression, and personality disorders with no psychotic background

Neuroleptics are, and have been, used for symptoms such as sleep disorders, anxiety and mild depression, and behavioral problems with no psychotic history. The negative effects of neuroleptic therapy have been scientifically documented for some of these conditions.

A few studies address sleep disorders, all of which show that benzodiazepines are more effective than neuroleptics. The documentation on anxiety disorders is limited, but research shows that the risks for serious side effects are greater than the benefits derived from treatment.

Studies of neuroleptic therapy for depression suggest that there is no reason, except for possible concurrent psychosis, to use neuroleptics in this patient group. Nor is there any reason to use neuroleptic therapy in patients who are often seen in primary care with mixed conditions of anxiety, dejection, and nonspecific physical symptoms. The data suggest that low doses of neuroleptics have an antidepressant effect, but given the fact that treatment for depression is frequently prolonged, it is unwise to subject patients to the risks for serious side effects when safer and more effective alternatives are available. Similarly, neuroleptics should not be used to treat personality disorders unless patients have coexisting psychotic symptoms.

Side effects

The greatest risks associated with neuroleptics concern their side effects. To some extent, these include general side effects associated with all pharmaceutical treatment, such as allergies and, not uncommonly, effects on the liver. Common side effects of neuroleptics include mouth dryness, blurred vision, increased appetite, and weight gain.

More feared, and unfortunately even more common, are the negative effects on muscle function and coordination, and the psychological side effects that are seriously disturbing for patients.

Muscular disturbances are caused by neuroleptics blocking nerve cells in the brain, and may be expressed as muscle contractions throughout the body, or only in the face, mouth, and tongue. They may also be expressed as general motoric agitation where patients rock restlessly back and forth and/or pace around. The problems may be similar to those experienced with Parkinson's disease, ie stiffness, tremors, and mobility problems. Other potentially pronounced muscle disturbances include involuntary movements such as habitual chewing, grimacing, sticking out one's tongue, or exaggerated arm and leg movement.

Muscle disturbances may appear during the acute phase of the disease when treatment is started or dosage is increased. Usually these side effects disappear if the neuroleptic dose is reduced and/or antiparkinson medication is used. Muscle disturbances also appear after prolonged use of medication. Particularly common are involuntary movements that do not always cease even after discontinuation of neuroleptic therapy. Approximately one fourth of the patients treated with neuroleptics for 5 years or longer are affected by such side effects, and in half of these patients the problems are permanent. These are severe side effects and a major reason for limiting neuroleptics to strict indications and the lowest possible dose.

A rare but potentially life-threatening side effect is the so-called malignant neuroleptic syndrome which, in addition to pronounced muscle stiffness, is characterized by high fever and disturbed consciousness. Most patients recover completely if the condition is detected early and neuroleptic therapy is discontinued.

Psychological side effects also cause patients major discomfort. Patients may experience a sense of uneasiness or experience their existence as if under a glass cover (Zombie sensation is another term used to describe this experience). Characteristics of this condition include slow thought processes, reduced emotional involvement, reduced energy, and possibly dejection. These side effects are considered to be the main reason why many patients discontinue their medication, or keep taking it with reluctance.

Neuroleptics, particularly at higher doses and in particularly disposed patients, may cause disturbances in cardiac rhythm, causing death in rare cases.

Economic aspects

The economic cost to society from psychotic diseases is high. In 1994, the costs for health care, sick leave, and early retirement attributed to psychoses totaled approximately 10 billion Swedish kronor (SEK), whereof the direct costs to the health services were approximately 5.5 billion SEK.

The cost for neuroleptics alone in 1994 was approximately 175 million SEK, whereof 115 million SEK was spent on patients with some form of psychosis. The cost of neuroleptics prescribed for indications other than psychosis was 60 million SEK in 1994.

The later types of neuroleptics that have appeared on the market in recent years have been prescribed with increasing frequency. If all psychotic patients received these new

drugs, the cost for neuroleptics would rise from the present 175 million SEK per year to approximately 1 billion SEK per year. The newer drugs have increased the pharmaceutical costs by approximately 40 million SEK per year.

The increased pharmaceutical costs might very well be justified from either a humanitarian or an economic perspective. To be justified, the new drugs must substantially, not marginally, improve the prognosis for psychosis and/or reduce side effects. However, studies have not satisfactorily shown the benefits of the newer drugs to be greater than the benefits of conventional drugs. Even if the newer drugs have fewer side effects, this has not been satisfactorily demonstrated in published studies. Clozapine is an exception in this context and has been effective where other neuroleptics have failed. Its use is however restricted, since it presents risks to bone marrow and requires extensive control.

Future opportunities for development

Intensive research is now under way to develop new antipsychotic drugs that are either more effective, or have milder side effects. Preliminary studies of many new substances show promising results, but these studies do not adequately assess the potential advantages of the new drugs as compared to the existing neuroleptics.

Ethical aspects

Neuroleptic therapy, given sometimes against patients' wishes, raises many important ethical issues. These issues are the focus of a forthcoming SBU report on ethics in psychiatry.

Conclusions

"Neuroleptics" is a term used to describe a group of antipsychotic drugs that are effective in treating schizophrenia and schizophrenia-like conditions, mainly in persons under 65 years of age who have not been ill for an extended period.

Scientific documentation shows that approximately one third of the patients with schizophrenia will be symptom-free, one third will improve, and one third will demonstrate no positive effects from neuroleptic treatment.

Research suggests that, when possible, 1 to 2 weeks should be allowed to elapse before treating first-episode psychotic patients. This length of time is required for observation and diagnosis, and evaluating the degree of spontaneous improvement.

Thereafter, the lowest effective dose of an established, standard drug should be used. The decision to initiate neuroleptic therapy in new patients should be made by a specialist in psychiatry. Generally, high-dose therapy is not supported scientifically since the antipsychotic effects of neuroleptics can be achieved at relatively moderate doses.

Neuroleptic therapy for schizophrenia should be combined and coordinated with other interventions involving the patient's family, as well as social, psychological, and psychotherapeutic support. The literature shows this approach improves the patient's prognosis in several respects, reducing the need for, and thereby the side effects of, neuroleptics.

Neuroleptic therapy is frequently accompanied by serious, sometimes permanent, side effects. Neuroleptics should therefore be reserved for patients with severe psychosis.

Agitated and demented elderly patients should not be treated with neuroleptics, unless they demonstrate pronounced psychotic symptoms. The reason for not treating this group is that neuroleptic therapy has not been shown to have an effect on symptoms such as yelling, aimless wandering, and general anxiousness.

The same applies to neuroleptic therapy in young mentally retarded patients and other children and adolescents, except for those demonstrating severe autism, Tourette's syndrome, and schizophrenia.

Similarly, no scientific evidence supports the use of neuroleptics for treating sleep disorders, anxiety, depression, delirium tremens, and heroin detoxification, since the marginal advantages from treatment are offset by serious side effects.

In Sweden, neuroleptics are frequently prescribed for indications which are not supported by scientific evidence describing the benefits for patients. This primarily concerns prescriptions for indications other than psychoses, and mainly prescriptions written within the network of services for the elderly. High doses of neuroleptics continue to be prescribed for treating psychoses, although the effects achieved by high doses are not found to be superior to the effects achieved by standard doses. New, and more expensive, drugs have increasingly been used without evidence to support superior effects or milder side effects. High doses do not only increase the risks in patients, but also waste resources.

There are therefore compelling reasons for the appropriate authorities and the psychiatric profession to actively engage in disseminating the findings of this literature review. Among other uses, it provides the foundation for recently published clinical guidelines on the use of neuroleptics. Continuing education programs must be developed to promote the application of these findings, particularly in psychiatry, family medicine, and geriatrics. Such efforts should substantially reduce the wide variations in practice currently found throughout Sweden.

It is essential to develop new drugs that are more effective in treating psychoses, but which do not possess the debilitating and movement-inhibiting side effects associated with traditional neuroleptics. New agents must be tested and compared with conventional treatment through controlled clinical trials, addressing the effectiveness, safety, and economic aspects of treatment. A network of psychiatric professionals should be established in order that such studies may be quickly and effectively conducted.

A collective effort is needed to make up for the lack of follow-up studies and syntheses to assess outcomes. Among other topics, there is a need to study how neuroleptics are best combined with other forms of treatment, and what organizational models best promote patient recovery.

Presumably, before major breakthroughs in treatment can be achieved, greater knowledge is needed about the origins of psychoses. Considering the prevalence of psychotic diseases, and the serious consequences for patients and their families, greater attention must be focused on the need for basic research and applied clinical research in this field. It is particularly important to invest in health services research, since neuroleptic therapy is always carried out within a health services organization, parts of which may be less than optimal.

Facts: Neuroleptics approved for use in Sweden

Buronil (melperon)
Cisordinol (zuclophentixol)
Dridol (droperidol)
Esucos (dixyrazine)
Fluanxol (flupentixol)
Haldol (haloperidol)
Hibernal (chlorpromazine)
Leponex (clozapine)
Mallorol (thioridazine)
Neulactil (periciazine)
Nozinan (levomepromazine)
Orap (pimozide)
Pacinol (fluphenazine)
Risperdal (risperidone)
Siqualon (fluphenazine)
Stemetil (prochlorperazine)
Theralen (alimemazine)
Trilafon (perphenazine)
Truxal (chlorprothixene)
Zyprexa (olanzapine)