PSYCHOTROPIC MEDICATION IN THE ELDERLY

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INTRODUCTION

Old age and disease are not synonymous[1]. On the other hand elderly people spend more money on healthcare than any other group because they *do* tend to have more health problems than any other group of the population.

The increasing elderly population may have resulted in an increased number of elderly patients requiring treatment for mental and behavioural disorders[2]. Pfeiffer[1] has concluded, through his own personal experience that 'in psychiatry, older patients are more responsive to treatment and intervention than any other age group.... but special considerations of changed circumstances - physiologic, psychologic and social must be made in proceeding to diagnose, treat and hopefully rehabilitate'. Indeed, a disproportionately large percentage of psychotropic medications are prescribed to the elderly, many of whom believe that their daily performance depends on the use of these drugs[3]. Moreover, there are relatively few clinical studies of the prescribing of psychotropic drugs, including sedatives, hypnotics, anxiolytics, antidepressants and neuroleptics in patients over 65 years of age, and also, few publications on the use of psychotropic drugs in the elderly.
The appropriateness of psychotropic drug therapy begins with careful diagnosis which, in the elderly, should be directed at treating the underlying causes and problem rather than merely responding to symptoms.

Anxiety states in elderly patients

Numerous factors, such as loss of friends and loved ones, failing health, intellectual decline, feelings of worthlessness and helplessness and loss of control over their immediate environment, make the elderly particularly susceptible to anxiety states. Anxiety and agitation may also be symptoms of a functional, psychiatric or organic or medical illness. Neurotic and depressive illness appear particularly frequently in aged populations with anxiety and agitation as sole complaints or combined with other psychiatric symptoms. Anxiety in the elderly frequently manifests itself in somatic form, with more restlessness, autonomic signs, agitation, insomnia and vague aches and pains. Although not all anxiety states need to be treated, on the other hand, disability and discomfort are two criteria that are useful for prescribers to decide when to use anti-anxiety drugs[4].

Anxiolytic therapy in the elderly

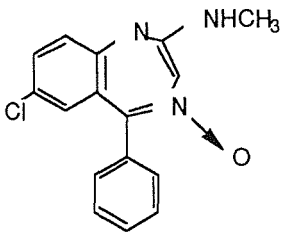
The currently most appropriate agents for generalised anxiety disorders, which account for up to 50% of all anxiety disorders recognised, are benzodiazepines and buspirone, with benzodiazepines being the drugs of choice[5,6].

Benzodiazepines work by enhancing the activity of the central neurotransmitter, gamma aminobutyric acid (GABA)[7].

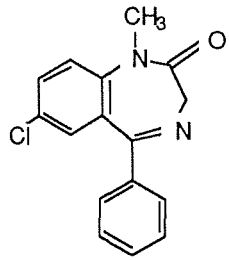
In view of the concerns about benzodiazepine dependence and serious side-effects, in 1988 the Committee on Safety of Medicines (CSM)[8,9,10] updated its 1980 guidelines. The CSM recommended that benzodiazepines as anxiolytics should be used for short-term relief (2-4 weeks only) for anxiety that is severe, disabling or subjecting the individual to distress; occurring alone or with insomnia or psychosomatic, organic or psychiatric illness. Particularly in the elderly, where there is evidence of increased sensitivity to benzodiazepines, consideration must be made of recommendations regarding pharmacological differences

between 'long'-acting benzodiazepines whose half-life exceeds 10 hours, e.g. diazepam, chlordiazepoxide and medazepam - and the 'short'-acting, rapidly cleared compounds such as triazolam, temazepam, oxazepam and lorazepam (Figure 1). The pharmacological properties of this latter group, including rapid excretion and lack of accumulation of the whole drug and active metabolites may offer certain advantages over the so-called 'long'-acting benzodiazepines, particularly in the elderly.

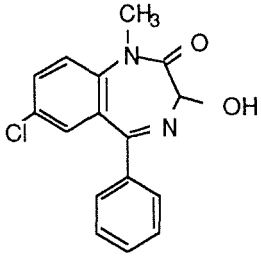
Fig. 1. Structural formulae and generic names of some 'short-' and 'long-' acting benzodiazepines



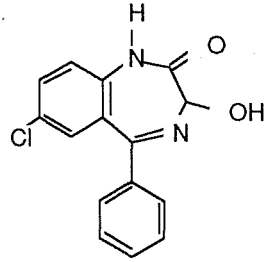
Chlordiazepoxide



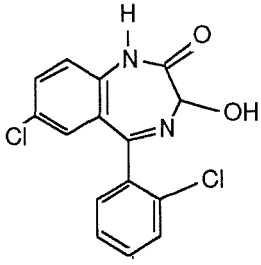
Diazepam



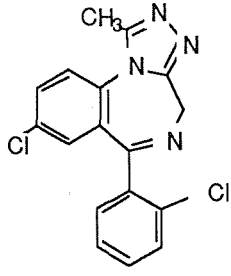
Temazepam



Oxazepam



Lorazepam



Triazolam

Table 1 shows the change of some psychotropic drug parameters with age, including those of some benzodiazepines, after Griffin[11], whilst Table 2 shows the results obtained by Greenblatt et al[12] from studies of the relation of age to the clearance of some psychotropics, including benzodiazepines, cleared by hepatic biotransformation where, it is evident, that age may effect hepatic oxidative processes to a greater extent than conjugative metabolic processes (also adapted from Griffin[11]).

Table 1
Change of some psychotropic drug parameters in the aged

Drug	Biological half-life	Volume of distribution	Total clearance
Amitriptyline	I	D	D
Chlordiazepoxide	I	I	D
Desipramine	I	NI	NI
Desmethyldiazepam	I	I	D
Diazepam	I	I	U or D
Imipramine	I	NI	NI
Levopromazine	I	U	D
Lorazepam	U or I	D	U or D
Nitrazepam	I		U
Nortriptyline	I	U	D
Oxazepam	I	I	NI
Protriptyline	I	D	D
Thioridazine	I	NI	NI

I = Increase
D = Decrease
U = Unchanged
NI = No information available

Adapted from Griffin[11]

Table 2
Studies of the relation of age to the clearance of some psychotropic drugs by hepatic biotransformation

Drug or Metabolite	Initial Pathway of Biotransformation
Evidence suggests age-related reduction in clearance	
Diazepam[b]	Oxidation (DA)
Chlordiazepoxide	Oxidation (DA)
Desmethyldiazepam[b]	Oxidation (OH)
Desalkylflurazepam[b]	Oxidation (OH)
Clobazam[b]	Oxidation (DA)
Alprazolam[b]	Oxidation (OH)
Nortriptyline	Oxidation (OH)
Small or negligible age-related change in clearance	
Oxazepam	Glucoronidation
Lorazepam	Glucoronidation
Temazepam	Glucoronidation
Nitrazepam	Nitroreduction
Flunitrazepam	Oxidation (DA) Nitroreduction
Data conflicting or not definitive	
Imipramine	Oxidation (OH, DA)
Amitriptyline	Oxidation (OH, DA)
Amobarbital	Oxidation (OH)

OH = Hydroxylation
DA = Dealkylation
b = Evidence suggests that the age-related reduction in clearance is greater in men than in women.

Adapted from Griffin[11] after Grenblatt et al[12].

Unwanted effects of benzodiazepines

The CSM noted that there is a particular lack of evidence that benzodiazepines were efficacious in anxiety after 4 months' treatment and recommended a warning on repeated prescriptions for an extended period of time.

It was also particularly concerned with withdrawal symptoms which because of their similarity with the symptoms of the original illness might suggest to the prescriber that treatment was inadequate and a further course was needed; of particular concern were the well-documented findings of unwanted residual daytime sedation seen during administration of 'long'-acting benzodiazepines where slow elimination leads to an accumulation of whole drug and active metabolitics. Such effects include drowsiness and impairment of coordination and judgement.

The committee noted the increase in the occurrence of adverse reactions of all kinds in the elderly. Such effects, often accompanied by confusion, occur particularly during drug treatment with long-acting benzodiazepines, where impaired liver and renal functions delay the elimination of drug and metabolites even further. It was suggested that the use of benzodiazepine therapy in the elderly, especially use of the long-acting benzodiazepines for insomnia be undertaken for short periods of time and only after careful consideration. Patients are to be carefully monitored during the treatment period.

Generally, the dosage recommendation for elderly patients is 1/2 adult dose and warning and adverse events for the elderly include their greater liability to experience, drowsiness, sedation, blurred vision, unsteadiness, ataxia (after single or repeated doses).

Trends of benzodiazepine usage in Maltese elderly population

Preca[13] has recently carried out an interesting study on the trends of benzodiazepine use in Malta. As part of this study a survey was carried out on residents of a 1000 bedded residence for the elderly, based on the Defined Daily Dose method; he concluded that 50% elderly were on benzodiazepines by day to control their anxiety and by night to control their insomnia. In another survey based on data obtained in 1989 for consumption figures held at the Health Department through the Narcotic and Psychotropics Control Card System, results showed that there was a significant increase in benzodiazepine use with age which was

ascribed to onset or increased anxiety disorders and/or concomitant ill-health (see Figures 2 and 3).

Fig. 2. Age distribution of benzodiazepine users (1989)

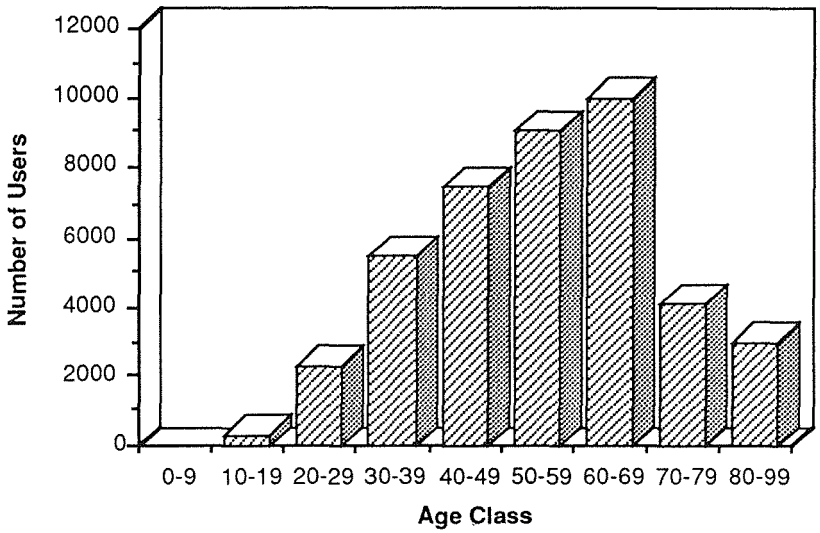
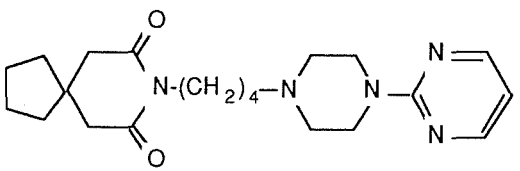


Fig. 3. Percentage benzodiazepine users per age class of Maltese population (1989)

A new class of anxiolytics

Concern about benzodiazepine dependency has encouraged renewed interest in Tricyclic Antidepressants and Monoamineoxidase Inhibitors in neurosis and has stimulated the development of new anxiolytic drugs acting on serotonin receptors. Buspirone is the first of a new class of anxiolytic agents known as azaspirodecanediones (Figure 4), which are chemically and pharmacologically unrelated to benzodiazepines, or to other anxiolytics[15]. The mechanism of action of buspirone differs from that of benzodiazepines in that it acts through a non-GABA mechanism. However, in man, details of its mechanism of anxiolytic action remain to be elucidated. From animal studies it is known that buspirone exerts a differential influence upon monoaminergic neuronal activity suppressing serotonergic activity while enhancing noradrenergic and dopaminergic cell firing[16]. Buspirone may offer hope for the elderly since the side-effects of benzodiazepines (e.g. sedation, confusion, ataxia and exacerbation of memory lapses) are particularly troublesome in this population and seem to be lacking with this agent. There still seems to be, however, a lack of sufficient data on buspirone in the elderly, on its long-term safety and efficacy, toxicity in overdose and use in other anxiety disorders[17].

Fig. 4. The structural formula of Buspirone



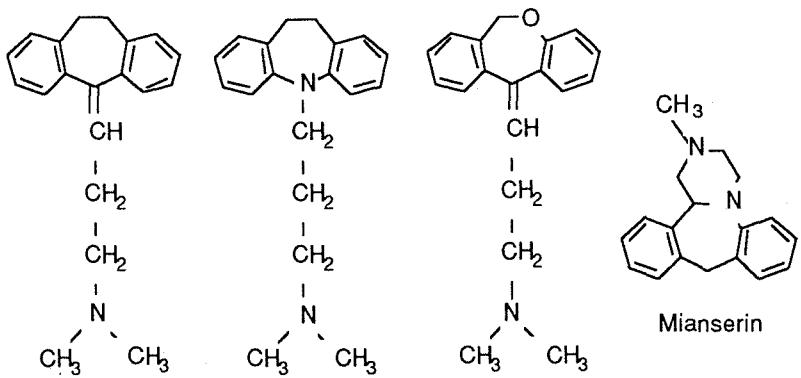
Buspirone

The treatment of depression in old age

Depression is the commonest mental disorder in 'younger' old patients, but its prevalence remains equally high in the 'old' old. All modern treatments which are used in younger patients have their place in management of old age depression[18]. These include the tricyclic anti-depressants (TCAs) such as amitriptyline and imipramine (Figure 5)

which act by blocking pre-synaptic uptake of the neurotransmitters norepinephrine and serotonin, at the nerve-endings thereby increasing the level of transmitter. Because of their rather non-selective effect however, there is a long list of side-effects associated with their use with mental confusion and constipation being the most common presenting symptoms and clinical manifestation in the elderly (See Table 3).

Fig. 5. Structural formulae and generic names of some more commonly used tricyclic antidepressants



Treatment should be initiated gradually especially in the elderly who because of a hypotensive effect of these drugs are prone to attacks of dizziness or even syncope. Drug interactions are also a problem.

The so-called 'tetracyclic' derivative mianserin (Figure 5) may be advantageous to use as it has fewer and milder anticholinergic and cardiovascular effects and many of the drug interactions of the TCA's are absent. On the other hand, mianserin has been associated with haematological and hepatic reactions. Consequently, patients being treated with these agents require careful supervision[20].

Table 3
Side effects of tricyclic antidepressants

Side effects	Symptoms include
Anticholinergic effects	- blurred vision - dry mouth - constipation - urinary retention - sweating
Cardiovascular effects	- hypotension - dizziness - tachycardia - myocardial depression - oedema
Gastrointestinal effects	- constipation (anticholinergic effect) - nausea, vomiting, heartburn
Neurologic effects	- confusion - drowsiness, sedation - muscle tremors, twitching, jitteriness - fatigue, weakness - hallucinations, delusions
Allergic effects	- rash
Other	- weight gain

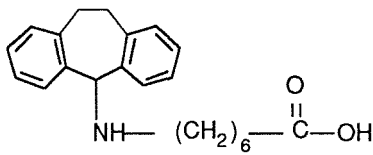
Adapted from Martindale[19].

A novel tricyclic antidepressant

A newer drug which does seem to hold promise for the treatment of 'later life' depression is amineptine, a recently developed psychotropic drug with psychostimulant and antidepressant properties. It is a TCA derivative with a novel chemical structure bearing a long 7-amino heptanoic acid chain[21](Figure 6). It shares the common features of TCAs

but is claimed to be unique in decreasing D_2-dopaminergic receptors after treatment. Studies in elderly subjects with a mean age of 80 years have shown no disorders of consciousness, no orthostatic symptoms and no arrythmia[22].

Fig. 6. The structural formula of Amineptine



Amineptine

New selective serotonin re-uptake inhibitors

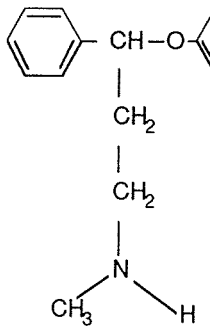
A series of selective serotonin re-uptake inhibitors (SSRIs) have recently been introduced clinically. While they may not necessarily be more effective then other antidepressants, their specificity means they are less likely to cause adverse reactions[23]. The SSRIs include fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram (Figure 7).

Feighner et al,[24] have pooled data from both double-blind and open-label studies in geriatric outpatients in the 60-82 age range to evaluate safety and efficacy of fluoxetine in DSM-III major depression. Fluoxetine is a newly designed molecule unrelated to TCAs chemically. It has also shown promise as a geriatric antidepressant having a lack of cardiotoxic effect and low lethality in overdose. It has compared equally well with such reference antidepressants as amitriptyline, doxepin (Figure 5) and imipramine in relieving the symptoms of depression with less anticholinergic effects such as dry mouth and constipation.

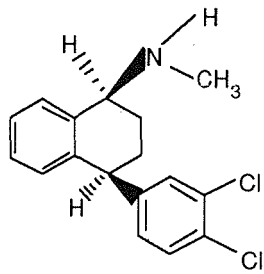
Moreover it was noticed that while amitriptyline caused a weight gain, fluoxetine did not. The other members of this group of SSRIs seem to share this property; in the elderly, a weight gain occurring during an antidepressant treatment, can aggravate concommitant cardiovascular disease, hypertension, diabetes or arthropathies[25,23]. Other studies have

shown that fluvoxamine and sertraline retain an unchanged pharmacokinetic profile in the elderly[23].

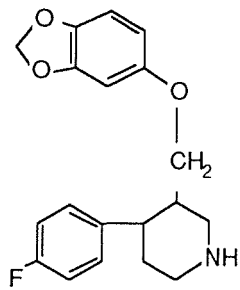
Fig. 7. Structural formulae and generic names of some more recently developed selective serotonin reuptake inhibitors



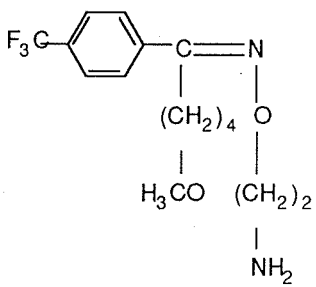
Fluoxetine



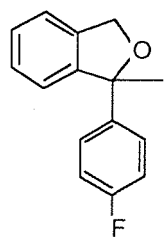
Sertraline

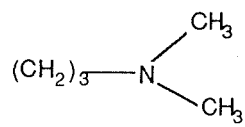


Paroxetine



Fluoxamine





Citalopram

SSRIs: interactions with MAOIs, lithium and tryptophan

The coadministration of SSRIs with other drugs which also increase serotonin function is potentially dangerous; whilst this may be beneficial in certain cases, their combinations can increase the severity of serotonin-related side-effects which can also be life-threatening[26]. Monoamine oxidase inhibitors (MAOIs) must not be given within two weeks of stopping SSRIs and because of the long half-life of fluoxetine

and its major active metabolite norfluoxetine, five weeks after stopping fluoxetine, before initiating a MAOI[23,27].

Suicidal tendencies

In 1990, the American Journal of Psychiatry reported that six patients suffering from depression had developed violent suicidal tendencies after two-seven weeks treatment with fluoxetine[23,28]. But an analysis of controlled studies of SSRIs found no evidence that these drugs actually increased suicide risk.

The incidence of suicide is 20-30 times greater in depressed persons than in the general population. Untreated severe depression of old age, carries a high risk of suicide and therefore, this possibility must be monitored. Indeed giving antidepressants, by relieving lethargy may activate suicidal thoughts.

It has been suggested that an increase in such thoughts is part of the natural history of depression. Paroxetine trials have suggested that, far from worsening suicidal tendencies, the drug tended to prevent their emergence[23].

The classical MAOIs - non-specificity and irreversibility

The Monoamine-oxidase Inhibitors (MAOIs) have been mentioned above. It is now over 30 years since the anti-tuberculosis drug Iproniazide (Figure 8) was found to be effective in relieving depression[29]. The mode of action of iproniazide is inhibition of the enzyme mono-amino-oxidase (MAO) responsible for the inactivation of the neurotransmitters norepinephrine and serotonin which - according to the amine theory - are found in too low concentrations in depressed patients. The inhibition of MAO with iproniazide results in higher concentration of noradrenaline and serotonin in the synaptic gap and at the post-synaptic receptors. Iproniazide is thus an MAOI. Together with the TCAs, MAOIs opened new possibilities of treating depressed patients. But compared to the TCAs, they have many drawbacks, including doubtful clinical efficacy, many interactions with other drugs and serious (even fatal) side-effects e.g. hypertensive crises, through inhibition of tyramine metabolism and / or interaction with sympathomimetic-

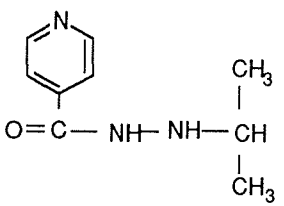
containing drugs. MAOIs are thus not first choice antidepressants but generally only used in therapy-resistant depressed patients.

MAOIs are also used by some psychiatrists in certain depressive and other disorders e.g. atypical depression, agoraphobia and panic anxiety. Others use MAOIs in combination with TCAs which, unless the utmost care is exercised, can result in serious interactions as explained above.

The 'classical' MAOIs are non-specific in that they inhibit both the A- and B- form of MAO-enzyme. The A- form is believed to be responsible for the inactivation of noradrenaline and serotonin whilst the B- form is believed to be responsible for dopamine degradation.

Moreover, the classical MAOIs perform a non-reversible inhibition of MAO-enzyme which is more or less destroyed and the inhibition lasts until a new enzyme is synthesized. This synthesis can e.g. in elderly depressed patients, take up to 2-3 weeks[30].

Fig. 8. The structural formula of Iproniazide



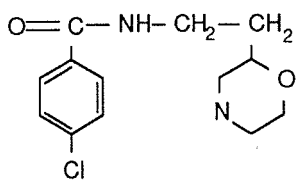
Iproniazide

New MAOIs: reversible inhibitors of MAO - A type

Moclobemide and brofaromine are 2 examples of newly-developed MAOIs with selective and reversible inhibition of monoamine oxidase, Type A moclobemide[31] is the first benzamide antidepressant [p-chloro-N-(2-morpholinoethyl) benzamide] (Figure 9). In long-term studies, over 500 patients were treated with this novel agent for more than four to six weeks, of whom one third were over 60 years of age and two thirds

were female; thus, the long-term patients were typical of the depressive population in general. No new adverse symptoms which had not been present during long-term therapy appeared during long-term treatment, and adverse events were generally infrequent. While a 'cheese effect' can never be excluded, as the inhibition of MAO-A may lead to a potentiation of the tyramine pressor effort, it has been shown that a tyramine-restricted diet is not necessary during moclobemide therapy and that age and depression have no influence on the interaction between moclobemide and tyramine; neither do elderly patients require a special dose adjustment. It has thus been concluded that moclobemide may be used over periods of months up to several years, even in elderly patients. Since treatment of depression in elderly patients is particularly difficult and complicated by disturbing side-effects (especially anticholinergic effects) the advent of a new well-tolerated antidepressant may be of great significance[32]. Further reports in the literature would be however needed to consolidate this conclusion.

Fig. 9. The structural formula of Moclobemide



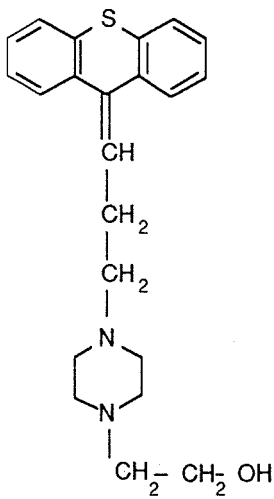
Moclobemide

Neuroleptics in institutionalized and non-institutionalised elderly

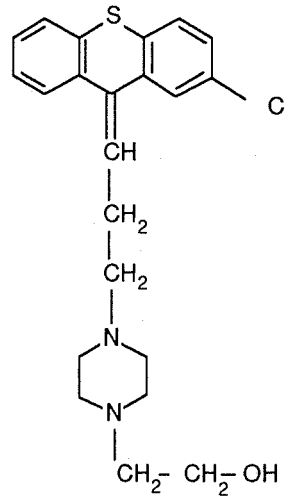
In Malta, a quarter of beds in the main psychiatric hospital are occupied by elderly (longstay) patients rather than by acute admission case, the most common diagnostic categories being schizophrenia and dementia together with affective disorders[33].

Institutionalized patients in psychogeriatric wards as also geriatric outpatients visiting psychiatric short-stay clinics are usually candidates for treatment with various psychotropic preparations including neuroleptics, although ideally, polypharmacy should be avoided.

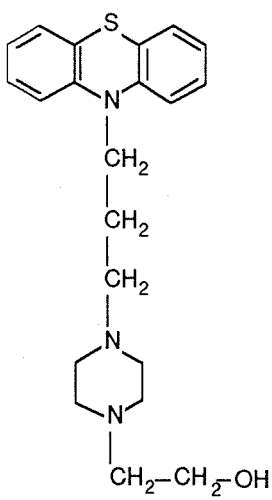
Fig. 10. Structural formulae and generic names of the neuroleptics used in the Olsen study



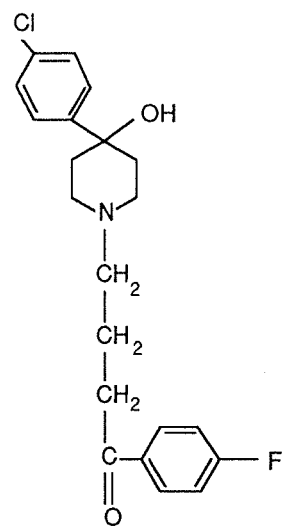
Flupenthixol



Zuclopenthixol



Perphenazine



Haloperidol

An important survey of prescribing and clinical outcome of psychotropic medication in the elderly was carried out by Olsen et al. in Denmark, in 1990[2] (Figure 10). This consisted of a prospective study which was undertaken at three centres caring for the elderly encompassing 160 patients over 65 years of age from general nursing homes and a psychiatric department.

The main reasons for initiating psychotropic medication were indicated, and amnestic data were collected. Initial and continuing dosages of psychotropic medication were recorded. The clinical condition was assessed at the start of treatment and after four to eight weeks, utilizing the Clinical Global Impression(CGI) scale. The patients' daily activity using the abbreviated Stockton Geriatric Rating Scale (SGRS) was assessed. Side effects were recorded using the UKU scale. Clinical improvement was seen in about half the patients with the best effect in patients with psychotic symptoms. Patients with dementia-related problems responded less well. Side-effects were few and generally mild. This situation was related to cautious introduction of the medication and adoption of low dose regimens.

It was further noted that out of 160 patients, 64 (4%) were suffering from dementia, 30 (19%) had paranoid states, 26 (16%) neurotic states and 15 (9%) had manic-depressive psychosis. The main reasons for treatment of the senile dementia group were symptoms of confusion, restlessness, aggressiveness whilst those in the paranoid group were clearly psychotic. Neuroleptics were the most used psychotropic group of drugs. Other drugs included antidepressants (TCAs) and hypnotics (oxazepam). Table 4 shows the distribution of patients by main drug groups and additional psychotropic medication. The neuroleptics used in this study included the thioxanthenes, zuclopenthixol and flupenthixol; the butyrophenone, haloperidol; and the phenothiazine, perphenazine.

Side effect profiles of psychotropics can be a major influence on the prescriber's choice of drug. This has been described by Schamoian[37] on the use of neuroleptics. It may be appropriate to accept mild side-effects in order to obtain an effective treatment[37]. By initiating and maintaining treatment with low dose regimens, few extrapyramidal side-effects and no orthostatic hypotension were observed in the Olsen study, whilst the most frequent side-effects observed were fatigue and sedation both of which have been previously described with neuroleptic treatment of elderly patients.

Table 4

Patients distributed by main drug groups and additional psychotropic medication

		Additional Psychotropic Medication				
Main Drug Group	No. of Patients	Neuro-leptics	Anti-Depressants	Sedatives	Hypnotics	% of patients with no additional psychotropic drugs
Neuroleptics	104	10	5	33	23	32.7
Anti-depressants	28	6	-	11	5	53.6
Sedatives	27	14	3	-	4	48.1
Hypnotics	1	1	-	-	-	-

After Olsen et al[2].

Antipsychotic potency of neuroleptics - the dopamine theory

It is well known that the antipsychotic potency of neuroleptics is closely related with their dopamine (DA) receptor blocking potency[34]. According to the affinity for both D-1 and D-2 receptors, neuroleptics can be divided into different groups.

Thioxanthenes have affinity for both D-1 and D-2 receptors; phenothiazines have affinity for D-2 receptors and considerably low affinity for D-1 receptors; and butyrophenones together with diphenylbutylpiperidenes, e.g. pimozide and benzamides e.g. sulpride, have affinity for only D-2 receptors. Although the clinical significance of the classification may be speculative, in several behavioural tests the D_1/D_2 classification has been observed and it has been suggested that D-1 receptor activation is responsible for dyskinesia. Since tardive dyskinesia (TD) is often claimed to develop after longterm treatment with neuroleptics it can be concluded that blockade of D-1 receptors may be advantageous. Furthermore, if TD is caused by the development of DA receptor hypersensitivity, the neuroleptics least capable of inducing this should be used. Thioxanthenes induce least tolerance and hypersensitivity and have been considered drugs of choice for long-term maintenance treatment. Whilst blockade by neuroleptics in general of other receptors including serotonin receptors, α-adrenoreceptors, histamine receptors, and muscarinic cholinergic receptors might contribute to the therapeutic effect, affinity to these receptors is often implicated in side-effects[35].

The optimal outcome of treatment

A reason for the frequent reports on side-effects in elderly patients could possibly be the use of different types of psychotropic drugs at the same time. Since many elderly patients are given medicines in connection with other diseases, it is necessary to attach closer attention to drug interaction. Possible pharmacokinetic changes in the elderly such as slower drug elimination or altered hepatic mechanism should influence the prescriber to use the lowest effective dosage to individual patients.

From a clinical point of view the overall risk/benefit balance is particularly important in the elderly, and the optimal outcome of treatment is

achieved by cautious introduction of psychotropic drug regimens and low dosages of the selected drugs[2].

Conclusion - the case for psychogeriatric pharmacy

In this context it is important to emphasise the role of pharmacists in helping elderly patients and their carers to understand their condition and to comply with prescribed medication. The community pharmacists will find themselves becoming increasingly involved with these kind of patients and should be vigilant for adverse drug events, drug interactions etc. The pharmacist in an institution can contribute to the refining of dose and avoidance of polypharmacy with the provisions of correct information to the physician and educating the patient to comply with his medication. However, if the profession is to rise to this challenge of responding to the needs of psychogeriatric patients and their carers, undergraduate and postgraduate curricula should equip pharmacists with sound knowledge of mental health including problems associated with the elderly; the major advances in psychopharmacology; psychological and social aspects of illness and treatment; and communication skills.

Close liaison with other healthcare professionals and collaboration with the clinical services are in the interests of the elderly patients and their families.

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