INTRODUCTION

The average life span in many parts of the world has increased over the past century beginning with new challenges. In India those above the age of 60 years form 6.4% of the country's population. This figure is likely to increase to 15% by 2025 A.D.

Community based studies have shown higher prevalence of psychiatric disorders in the elderly. Ramchandran et al. (1982) reported 35% from a survey conducted in a suburban area near Chennai. Venkoba Rao and Madhavan (1982) reported 8.9% from the Thiruppuvanam survey.

A retrospective study of geriatric patients attending tertiary care psychiatric hospital (IPHB) at Goa revealed psychotic illness in > 70% of geriatric patients attending the outpatient department for the first time (Yvonne da Silva perira et al. 2002). A single institutional retrospective study of 3 years to assess socio-demographic characteristics and pattern in elderly outpatients revealed 48.07% mood disorders, 15.47% neurotic and stress related disorders, 6.08% schizophrenia, 14.36% organic psychosis, 4.97% persistent delusional disorders and 6.08% unspecified non-organic psychosis (Gurvinder et al. 2004).

Psychosis in elderly patients is a growing clinical concern because psychotic symptoms most frequently occur as non-cognitive manifestations of Alzheimer's disease, as a side effect of drug therapy for Parkinson's disease, or as the primary abnormalities in schizophrenia, and the clinical characteristics of psychosis are distinct for each. In planning antipsychotic pharmacotherapy for elderly patients, age related pharmacokinetic changes, Poly-pharmacy for co-morbid diseases and concerns about the underlying conditions responsible for the psychotic symptoms must be considered. Psychotic symptoms can be associated with aggressive or disruptive behavior (Gilley et al. 1997) and are often a source of distress to caregivers (Zarit et al., 1986). They can result in neglect and abuse of elderly patients (Steele et al., 1990) and persistent symptoms often result in institutionalization.

A number of factors have been hypothesized to contribute to an increased risk of psychosis in elderly people. They are - age related deterioration of frontal and temporal factors, neurochemical changes associated with ageing, social isolation, sensory deficits, cognitive decline, age related pharmacokinetic and pharmacodynamic changes and polypharmacy (Targum and Abbott, 1999; Steven D. Targum, 2001).

Over the years, many new molecules have been examined regarding their antipsychotic properties and a huge literature has been gathered. On the other hand data regarding individual based and family based psycho-social interventions have also accumulated so there is a compelling need to review all such data to see where we stand as far as global scientific data base is concerned. Simultaneously we also need to see from the point of view of our country i.e. whether and how our unique circumstances suggest any differences to be considered in the management of psychosis in elderly patients.

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These guidelines seek to summarize data available on major treatments available for elderly with psychosis, with the hope that this knowledge will help ensure uniform standards of care.

Psychiatrists caring for a patient should consider, not getting limited to the recommendations made. It should be emphasized that observations and opinions made in this review are only general guidelines and the exact and the best treatment in an individual case have to be based on a number of considerations unique to that case. As it is a preliminary effort due to paucity of previous work in this area in India, it is expected that several revisions and modifications will be required to improve its usefulness.

**Classification and Clinical Presentation**

Among elderly patients psychotic symptoms can be seen in a wide range of conditions. The causes and clinical manifestation of the symptoms usually vary with the underlying condition. Psychotic symptoms of acute onset are usually seen in delirium secondary to medical condition, drug misuse and drug induced psychosis. Chronic and persistent psychotic symptoms may be due to a primary psychotic disorder (chronic schizophrenia, late onset schizophrenia, delusional disorders, and affective disorders), psychosis owing to neurodegenerative disorders (Alzheimer's disease, vascular dementia, dementia with Lewy bodies and Parkinson's disease) or chronic medical conditions.

**DSM IV Diagnosis Associated with Psychosis in the Elderly (Ronald L. Martin, M.D. 1997)**

<table>
<thead>
<tr>
<th>DSM IV Diagnosis</th>
<th>Related disorders</th>
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<tr>
<td>Delirium</td>
<td>Schizophrenia</td>
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<tr>
<td>Delusional disorders</td>
<td>Mood disorder</td>
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<tr>
<td>Dementia (every type)</td>
<td>Substance abuse</td>
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<tr>
<td>Metabolic disturbances</td>
<td>Chronic medical conditions</td>
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<td>Neurological conditions</td>
<td>Drug induced psychosis</td>
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**ICD-10 Diagnosis that may cause psychosis in elderly (Salman et al. 2005)**

<table>
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<tr>
<th>ICD-10 Classification</th>
<th>Related disorders</th>
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<tr>
<td>Schizophrenia</td>
<td>Late onset schizophrenia</td>
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<td></td>
<td>Persistent delusional disorders</td>
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<td></td>
<td>Acute and transient psychotic disorders</td>
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<td></td>
<td>Induced delusional disorder</td>
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<td></td>
<td>Schizoaffective disorders</td>
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<tr>
<td>Mood (Affective)</td>
<td>Manic episode</td>
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<td></td>
<td>Bipolar affective disorder</td>
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<tr>
<td></td>
<td>Depressive episode</td>
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<td></td>
<td>Recurrent depressive disorder</td>
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<tr>
<td>Dementia</td>
<td>Alzheimer's disease</td>
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<td></td>
<td>Vascular dementia</td>
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<td></td>
<td>Pick's disease</td>
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<td></td>
<td>Creutzfeldt - Jacob disease</td>
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<td>Huntington's disease</td>
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<td>Parkinson's disease</td>
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<td>HIV</td>
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<td></td>
<td>Head trauma</td>
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<tr>
<td>Delirium</td>
<td>All causes</td>
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The focus of this review is on psychosis in elderly patients with Alzheimer's disease, Parkinson's disease, schizophrenia, delusional disorder and bipolar disorders only.

REVIEW OF TREATMENT MODALITIES

A. Schizophrenia

Schizophrenia in elderly patients most often represents the continuation of a chronic condition that arises in adolescence or young adulthood, in a sizeable minority of cases; however, the onset of psychotic symptoms occurs later (more than 40 years of age) in life.

Evidence based review of treatment for younger adults who had schizophrenia, combined with general reviews of treatment for older adults who have had schizophrenia (Tune et al., 2003; Sable JA et al., 2002; Salzman et al., 2001) indicate that antipsychotic drugs coupled with psychosocial interventions should be the mainstay of treatment for persons who have schizophrenia. There has been much debate about the nosology and classification of schizophrenia in elderly. Some emphasize the similarities between early and late onset illnesses and some others highlight the difference in etiology, phenomenology and outcome. A consensus on nomenclature was reached in 1998, at a meeting of the International Late onset Schizophrenia Group (Howard et al., 2000). On the basis of the research evidence on symptoms, family history, brain imaging studies and the nature of the cognitive deficits observed, it was agreed to retain the word schizophrenia for the both early and late onset illnesses. However, the late onset was further subdivided into late onset (onset after 40 years of age) and very late onset often after 60 years of age (Salman Karim et al., 2005).

Sensitivity to antipsychotic medications has been identified in a number of treatment studies of late onset psychosis, and this necessitates a cautious approach by the clinician in considering this treatment option (Howard et al. 1992, Jeste et al., 1993, Sciolla et al., 1998).

Extra pyramidal and anti-cholinergic side effects and drug interactions, are more common than in younger patients, resulting in significant morbidity. In addition, risk of tardive dyskinesia is markedly greater in elderly patients taking antipsychotic medication (Sciolla et al., 1998, Jeste et al., 1993).

PHARMACOLOGICAL TREATMENT

a) FGAM's (First generation antipsychotic medications)
b) SGAM's (Second generation antipsychotic medications)

NON-PHARMACOLOGICAL TREATMENT

a) Electroconvulsive therapy
b) Cognitive Behavioral therapy
c) Psychosocial therapies

Antipsychotic medications

Schneider (1990), in a meta-analysis of seven placebo controlled trials of the use of typical antipsychotics, reported significant but modest efficacy. Devanand et al (1998), in a randomized placebo controlled dose comparison trial of haloperidol, reported superior efficacy of doses of 2-3 mg/day, with moderate to severe extra pyramidal symptoms occurring in 20% of patients; a lower dose was no better than placebo.
6 double blind randomized clinical trials evaluated the effectiveness of antipsychotic agents for older patients who had schizophrenia. Braichy et al. (1978) and Ruskin et al. (1991) examined the effectiveness and safety of conventional antipsychotic agents. Out of these the first study had small sample and the second study did not evaluate the side effects of efficacy of drug treatment for controlling psychopathology and improving functioning of the patients.

Howanitz et al. (1999) (Clozapine 300 mg/d v/s chlorpromazine 600 mg/d) and Kennedy et al. (2003) (Olanzapine 12 mg/d v/s haloperidol 10 mg/d) compared the treatment results of atypical antipsychotic agents with conventional antipsychotic and revealed improvement in psychiatric symptoms in all patients but SGAM’s have superior efficacy and a better side effect profile especially regarding EPS.

Harvey et al. (2003) compared the effectiveness of olanzapine with risperidone. The results showed no differences in efficacy and side effect profile of the two drugs except for greater weight gain with olanzapine.

Several open-label RCT’s indicates that SGAM’s were associated with less Parkinsonism and a greater improvement in negative and depressive symptoms in patients who were previously on FGAM’s (Barak et al. 2002(a), Ritchie, 2003, Davidson et al. 2000, Madhusoodanan et al. 1999, Barak et al. 2002(b), Ciudad et al. 2004, Kay et al. 1987)

Various single-agent open label studies evaluated the use of FGAM’s and SGAM’s in treating elderly schizophrenic patients (Madhusoodanan et al. 2004; Saitz et al., 2004; Sajactovic, 1998, Jeste et al., 1999, Tariot et al., 2000, Yeung et al., 2000, Lasser et al., 2004).


Antipsychotic drugs in Very Late Onset Schizophrenia (65+) evidence Base doses

Generally, the dosing of antipsychotic agents began at low levels and then increased to a targeted level. Mean doses of antipsychotic used in various studies are as follows -

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Mean dose</th>
<th>Studies reviewed</th>
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<tbody>
<tr>
<td>Haloperidol</td>
<td>7.2 to 9.4 mg/day</td>
<td>Kennedy et al 2003</td>
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<td>Barak et al 2002</td>
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<tr>
<td>Chlorpromazine</td>
<td>600 mg/day</td>
<td>Howanitz et al 1999</td>
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<tr>
<td>Fluphenazine</td>
<td>28.5 mg/day</td>
<td>Branchey et al 1978</td>
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<tr>
<td>Thioridazine</td>
<td>5 mg/day</td>
<td>Branchey et al 1978</td>
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<tr>
<td>Risperidone</td>
<td>1.7-2.0 mg/d</td>
<td>Branchey et al 1978</td>
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<td></td>
<td></td>
<td>and Ritchie et al 2003</td>
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<tr>
<td>Olanzapine</td>
<td>9.9-13.1 mg/d</td>
<td>Kennedy et al 2003,</td>
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<td>Harvey et al 2003</td>
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<td>Barak et al 2002</td>
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<td></td>
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<td>Ritchie et al 2003</td>
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<td></td>
<td></td>
<td>Ciudad et al 2004</td>
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<tr>
<td>Clozapine</td>
<td>300 mg/d</td>
<td>Howanitz et al 1999</td>
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DISCUSSION

The discussions about the use and safety of antipsychotic will probably go on for some time, but these have highlighted the need for research on alternative forms of treatment. For the present, it is important to be careful not to do more harm than good when initiating antipsychotic medication for older people and to follow the principle 'start low and go slow'.

Antipsychotic medications are the most widely used pharmacological treatment for both early- and late-onset schizophrenia in elderly people. Although there is a dearth of well-conducted studies (with few randomized controlled trials), there is some evidence that these drugs improve acute symptoms and prevent relapse (Jeste et al. 1996).

First Generation Antipsychotic Medications (FGAM's)

The research literature on the use of conventional antipsychotic in elderly people with schizophrenia is sparse and there are very few recent studies. Significant improvement in psychotic symptoms with the use of haloperidol, trifluoperazine (10-30mg/day) and thioridazine (40-50 mg/day) was reported in studies carried out in the 1960s (Post, 1966; Tsuang et al., 1971). Thioridazine has since been shown to cause prolongation of the QT interval and its use in elderly people is not recommended.

Depot antipsychotic medication can be useful in elderly patients who have problems adhering to medication regimens. Howard & Levy (1992) reported that low doses of depot antipsychotic (14.4 mg of flupenthixol decanoate or 9 mg of fluphenazine decanoate every 2 weeks) were associated with improved adherence and treatment outcome compared with oral medication.

Second Generation Antipsychotic Medications (SGAMs)

The newer atypical antipsychotic are currently considered the first-line treatment for older patients owing to their better side-effect profile in comparison with conventional antipsychotic (Tune & Salzman 2003). However, limited data are available from controlled trials showing their efficacy and safety in older people.

Clozapine

The usefulness of clozapine for treatment-resistant early-onset schizophrenia is well established, but concerns about toxicity and the need for monitoring white cell counts has led to limited use in older patients. clozapine's efficacy in refractory cases and its lack of neurological side effects with suppression of abnormal involuntary movements make it a unique neuroleptic with advantages over conventional antipsychotic agents. The drug appears to be safe when treatment is accompanied by frequent clinical and hematologic monitoring (Small et al. 1987). Clozapine at a relatively low mean dose seems to be safe, tolerated, and effective in elderly psychiatric patients; and agranulocytosis is more frequent than in younger adults and should be monitored carefully (Barak et al., 1999; Chengappa et al., 1995; Oberholzer et al., 1992). A few small studies on its use at lower doses in this population have reported sedation, lethargy and postural hypotension as common side-effects (reviewed by Barak et al. 1999). In their review Barak et al concluded that most showed moderate-to-marked improvement of psychotic features at a relatively low mean dose of 134 mg/day, but cautioned that agranulocytosis may occur more frequently in older people. In light of these risks, clozapine is not a first-line antipsychotic for elderly patients and should probably be used only in cases of treatment resistance and severe tardive dyskinesia (Howard et al. 2002; Sajatovic et al. 1997). Moeller et al.,
(1995) found no effect of substance abuse or dependence, diagnosis, or age on outcome in the overall patient group while studying risk factors for discontinuation of clozapine treatment. Clozapine and olanzapine have similar general antipsychotic efficacy and that risperidone may be somewhat less effective. Clozapine was the most effective treatment for negative symptoms. However, the differences among treatments were small (Volavka et al., 2002). Bilder et al. (2002) studied the Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder and found that Patients with a history of suboptimal response to conventional treatments may show cognitive benefits from newer antipsychotic drugs, and there may be differences between atypical antipsychotic drugs in their patterns of cognitive effects.

Risperidone and Olanzapine

Of the atypicals, risperidone is the most extensively studied drug in the elderly population. It is effective, well tolerated in low doses (1.5—6 mg/day) and produces significant clinical improvement in elderly people with schizophrenia (Katz et al, 1999; Madhusoodanan et al, 1999). Limited data are available on the use of olanzapine in treating older people with schizophrenia. Madhusoodanan et al (1999) compared 151 hospitalized elderly psychiatric patients (mean age 71 years) who received either risperidone or olanzapine. Olanzapine therapy was found to be effective, with side-effects reported in 17% of the patients, and the authors concluded that the drug was safe and effective in that population. Sajatovic et al. (1998) studied olanzapine in an open-label trial with 22 older patients with schizophrenia. They found that it significantly improved symptoms of schizophrenia and had few extra pyramidal side-effects without adversely affecting co-morbid medical problems. Owing to recent concerns about the side-effects of these two antipsychotic in people with dementia, their use is also likely to be restricted in people with schizophrenia. Elderly patients with aggravation of chronic schizophrenia may show clinically meaningful change in positive and negative psychotic symptomatology but not in depressive symptoms after being switched to olanzapine from previous neuroleptic treatment with no weight gain (Barak et al., 2004). After treatment failure with an atypical agent or haloperidol in treatment-resistant schizophrenia, a switch to olanzapine may not reduce psychopathology in general, but may improve symptoms related to cognitive function (Lindenmayer et al., 2002). Meehan et al (2002) evaluated the use of the new intramuscular preparation of olanzapine in patients with dementia with acute agitation in a double-blind study comparing dosages of 2.5 mg and 5 mg to lorazepam 1 mg and placebo. They found sustained benefit in terms of reduced agitation at 2 hours and at 24 hours for both olanzapine dosages in comparison to placebo, and sustained benefit at 24 hours in comparison to the lorazepam group.

The effects of risperidone and olanzapine on cognitive functioning in patients with schizophrenia were compared in a randomized, double-blind trial by Harvey et al. (2003) and Harvey and Napolitano et al. (2003). Atypical antipsychotic treatment is associated with wide-ranging benefits on cognitive functioning. The safety and efficacy of risperidone and olanzapine were compared in a double-blind trial that used doses widely accepted in clinical practice. Both treatments were well tolerated and efficacious. The frequency and severity of extra pyramidal symptoms were similar in the two treatment groups. Greater reductions in severity of positive and affective symptoms were seen with risperidone than with olanzapine treatment among study completers. There was no measure on which olanzapine was superior. Greater weight gain was associated with olanzapine than with risperidone treatment (conley and mahmoud, 2001). Olanzapine appears to be more efficacious in maintaining control over
negative symptoms in older patients with schizophrenia and related psychotic disorders in comparison to risperidone (Feldman et al., 2003).

Risperidone is more efficacious than haloperidol for affective symptoms in patients with schizophrenia (Peuskens et al., 2000). Risperidone appears to be an effective and well tolerated antipsychotic for elderly patients with chronic psychosis (Sajatovic et al., 1996).

A long-term, multicenter, open-label study of risperidone in elderly patients with psychosis long-term treatment with risperidone was associated with continued symptom improvement, a decrease in the severity of preexisting EPS, and a low incidence of TD in elderly psychotic patients (Davidson et al., 2000).

Quetiapine

On the basis of their review of the literature it has been suggested that quetiapine is safe for use in elderly people and is not associated with weight gain. To avoid the common side-effects of postural hypotension, dizziness and agitation, they recommend starting with the lowest possible dose (25 mg) and slowly titrating up to 100-300 mg/day. More recently, Jaskiw et al. (2004) in a multicentred open-label trial, have reported safe use in dosages up to 750 mg/day, given in divided doses. As no other study has reported use of quetiapine in such high doses for elderly people, we suspect that only an occasional patient would require a very high dose. Zhong et al. (2004) recently presented results of a randomized, placebo-controlled trial looking at dosages of quetiapine at 100 mg and 200 mg versus placebo in patients with AD with psychosis and behavioral disorder. The 200-mg dose appeared to offer increased efficacy compared to both placebo and the 100-mg dose. No increased risk for cerebrovascular adverse events in this treatment group was found.

Aripiprazole

The latest of the atypical anti-psychotics, aripiprazole with its unique mode of action, as a partial agonist at D2 receptors can be effective in improving both positive and negative symptoms. Furthermore, it is less likely than the other atypical to cause extra pyramidal symptoms, sedation, weight gain and cardiovascular side-effects (Hirose et al., 2004). It probably holds promise for both young and older people with schizophrenia, but there is less few data on its use, safety and dosing strategies in older people. Madhusoodanan et al. (2004) described their clinical experience of aripiprazole in ten elderly people with schizophrenia. They concluded that it is safe, improved both positive and negative symptoms and caused fewer side-effects. De Deyn et al. (2003), Breder et al. (2004) and Streim et al. (2004) used flexible-dose (2-15 mg/day) with mean dosing of about 10 mg per day. Significant improvement was seen in the treated groups on some, but not all, measurements of psychosis. An open-label study of aripiprazole in patients with drug-induced psychosis of Parkinson's disease, Fernandez et al. (2004) concluded that initial results were mixed but not encouraging.

Ziprasidone

There are no controlled studies of ziprasidone in elderly patients with dementia and secondary psychiatric symptoms. Studies of the use and efficacy of ziprasidone in the elderly are pending. Intramuscular (i.m.) ziprasidone after an initial dose of 10-20 mg (maximum daily dose: 40 mg), in elderly patients suggests acceptable safety and efficacy in the management of acute psychotic agitation among elderly patients with schizophrenia Barak et al. (2006)
NON-PHARMACOLOGICAL MODALITIES

a) Electroconvulsive therapy

Most research on the use of electroconvulsive therapy (ECT) on elderly patients with schizophrenia was conducted during the 1950s and 1960s. Kay & Roth (1961) reported temporary remission following the use of ECT or neuroleptics in about 25% of their patients. A better response to ECT in patients with late paraphrenia presenting with prominent affective symptoms was reported by Frost (1969). It appears that, with the introduction of a variety of typical and atypical antipsychotics, the use of ECT in elderly patients with schizophrenia has declined in clinical practice. Combining clozapine with ECT has been found safe and effective in patients resistant to classical antipsychotic agents, clozapine, or ECT alone (Kupchik et al., 2000, Kales et al., 1999).

Clozapine not only reduce psychopathology but also reduce service cost and improves quality of life due to reduction of need for hospital services. These benefits are observed after two tears of clozapine therapy (Revicki et al. 1990; Meltzer et al. 1990).

b) Cognitive-behavioral therapy

The usefulness of cognitive-behavioral techniques in modifying delusional beliefs and controlling hallucinations has been widely reported in younger people (Garety & Fowler, 1994). Unfortunately, there have been few attempts to study their use with elderly patients. Aguera-Ortiz et al (1999) have suggested that they might help elderly people gain insight into their illness and provide them with coping strategies to help them live a meaningful life.

McQuaid et al (2000) have developed a novel intervention for older people with schizophrenia that integrates cognitive-behavioral techniques and social skills training. This approach suits the needs of elderly people and aims at reducing their cognitive vulnerabilities and improving their ability to cope with stress and to adhere to other forms of treatment.

c) Psychosocial therapies

The effectiveness of psychosocial interventions in improving independent living and social skills in younger people with schizophrenia is well established (Kopelowicz & Liberman, 1998). Such interventions may also be of importance for elderly patients, a significant number of whom fail to show a complete response to antipsychotics (Howad, 2002). Bartels et al (2004), in a pilot study of elderly people with severe mental illness, found that a combination of interpersonal and independent skills training, together with standard occupational therapy, was associated with improved social functioning and independent living.

B. Neurodegenerative disorders

Among the neurodegenerative disorders, psychotic symptoms are commonly seen in Alzheimer’s disease, dementia with Lewy bodies and Parkinson’s disease. In Alzheimer’s disease and Lewy body dementia, psychotic symptoms are thought to be related to the underlying pathophysiology of the condition. In Parkinson’s disease, which commonly presents with motor symptoms and dementia, anti-Parkinsonian medication is the most frequent cause of psychotic symptoms.

B-I. Alzheimer’s disease (AD)

The prevalence of psychosis in people with Alzheimer’s disease ranges between 30 and 50% (Jeste
& Finkel, 2000). Bassiony et al (2000), in a community-based study of Alzheimer's disease, reported that about one-third of the participants showed evidence of psychotic symptoms and that delusions were more common than hallucinations.

The question of whether delusions in Alzheimer's disease are secondary to the cognitive deficits or are true psychotic phenomena remains unanswered. Hallucinations in Alzheimer's disease can occur in any sensory modality, but visual and auditory hallucinations are the most common (Tariot, 1995). There is some evidence of the association of psychotic symptoms with a rapid decline in cognition in Alzheimer's disease (Forste et al. 1994).

**CLINICAL PRESENTATION**

In a community based study of patients with presumed AD, one third showed evidence of psychosis, with delusions reported more often than hallucinations (Zimmer et al. 1984; Wragg et al. 1989; Tariot et al, 1993).

Complementing these findings a study of 329 patients with AD but no psychosis at base line showed that half of them developed psychotic symptoms within 4 years. (Paulsen et al 2000).

Global agitation or aggressiveness, however, may be harder to manage safely and may necessitate pharmacologic intervention. The decision to introduce psychotropic medications must be examined within the context of the total medical presentation of the patient, including co-morbid medical illnesses and concomitant medications. It has also been suggested that cholinesterase inhibitor drugs may have anti psychotic effects as well.

1. **Pharmacological treatment of psychosis in A.D.**

a) **Antipsychotics**

Antipsychotics have been the most widely used form of treatment for psychosis in Alzheimer's disease (Margallo-Lana et al. 2001), although not without concerns about the safety of their use, as discussed above. A number of fairly recent studies have demonstrated the efficacy of antipsychotics in controlling psychotic symptoms. However, most of these were designed to look at the usefulness of these drugs in controlling the behavioral and psychological symptoms of dementia, not its psychotic symptoms.

Schneider (1996), in a meta-analysis of seven placebo-controlled trials of the use of typical antipsychotics, reported significant but modest efficacy. Classical antipsychotic drugs now appear to be contraindicated with the advent of the atypical antipsychotic agents. Despite the paucity of well-controlled studies, those to date would indicate that the atypical antipsychotics are efficacious and well tolerated by elderly patients. Clozapine, however, with its potential for agranulocytosis and adverse autonomic effects, would seem to be the atypical of last resort. (Richard ET AL., 2000)

Devanand et al (1998), in a randomized placebo-controlled dose-comparison trial of haloperidol, reported superior efficacy of doses of 2-3 mg/day, with moderate-to-severe extra pyramidal symptoms occurring in 20% of patients; a lower dose (0.5 0.75 mg/day) was no better than placebo.

Of the atypical antipsychotics, there have been a number of randomized placebo-controlled trials of risperidone and olanzapine.

Katz et al (1999), in a randomized double-blind trial comparing risperidone with placebo in nursing-
home patients, demonstrated the efficacy of risperidone over placebo; the optimal dose was 1 mg/day. Other studies (De Deyn et al. 1999; Brodaty et al., 2003) have confirmed the efficacy of low doses of risperidone for controlling psychotic symptoms in Alzheimer’s disease.

Olanzapine in a dose of 5 mg/day significantly improved psychotic symptoms in Alzheimer’s disease in a double-blind placebo-controlled trial of 6 weeks’ duration. Higher doses (10 and 15 mg) showed no added benefit. Quetiapine in a dose of 100-300 mg/day has been reported to be well tolerated and to improve psychotic symptoms and hostility in people with Alzheimer’s disease (McManus et al., 1999; Tariot et al., 2000; Yeung et al., 2000).

Chacko et al. (1995) studied Clozapine for acute and maintenance treatment of psychosis in Parkinson’s disease, revealed significant resolution in psychotic symptoms and improvement in global behavioral status observed in all cases, with 10 patients maintaining improvement at follow-up. Careful initiation and titration of the drug resulted in few side effects, and dementia was not found to be a contraindication to such treatment.

b) Cholinesterase inhibitors

These are routinely used for cognitive deficits in Alzheimer’s disease, and more recently their possible usefulness in improving psychotic symptoms has been investigated. Although there have been no prospective double-blind studies, reviews of current data (most studies have been on rivastigmine, donepezil and galantamine) suggest that these drugs are well tolerated and may be of value in preventing or reducing psychotic symptoms in Alzheimer’s disease (Finkel, 2004; Wynn & Cummings, 2004).

B-II. Dementia with Lewy bodies (LBD)

Dementia with Lewy bodies is probably a part of the spectrum of Lewy body disorders. Its clinical presentation usually varies according to the site of Lewy body formation and associated neuronal pathology. Psychotic symptoms are seen more frequently in Lewy body dementia than in Alzheimer’s disease. Visual hallucinations are the most common symptom and have been reported in up to 80% of cases; other classic symptoms include fluctuating cognition, Parkinsonian motor symptoms, frequent falls and sensitivity to neuroleptic medications. Auditory hallucinations and paranoid delusions are also common, with prevalence rates of 20% and 65%, respectively (McKeith et al., 1996).

The treatment of psychotic symptoms in Lewy body dementia remains a challenge and most often requires a treatment-plan tailored to the characteristics of individual patients. This should strike a balance between the use of anti-Parkinsonian medication, which improves motor disorder but may induce psychotic symptoms, or not treating motor symptoms and cautiously treating the psychotic symptoms. This challenge also highlights the importance of non-pharmacological interventions.

Pharmacological treatment in LBD

a) Antipsychotics

People with Lewy body dementia are extremely sensitive to antipsychotics. Small doses can lead to extreme worsening of Parkinsonian symptoms, and about 50% of individuals experience
life threatening adverse effects (McKeith et al, 1992). Severe reactions may be dose related (Byrne et al. (1992). The above-mentioned adverse effects of neuroleptics in older people have discouraged their use and consequently no robustly designed studies of antipsychotics in Lewy body dementia have been carried out. However, some reports on the use of olanzapine in this population have been published (Walker et al., 1999; Cummings et al, 2002).

b) Cholinesterase inhibitors

A number of studies have reported improvement of psychotic symptoms with the use of cholinesterase inhibitors in Lewy body dementia. A large multicentre double blind trial comparing rivastigmine with placebo showed significant improvements in delusions and hallucinations. Beneficial effects of the use of donepezil have also been reported (Fergusson & Howard, 2000).

B. III Parkinson's disease (PD)

Psychotic symptoms in Parkinson's disease are most commonly extrinsic (resulting from treatment with anti-Parkinsonian drugs) and only occasionally intrinsic (secondary to the neurodegenerative process involving dopamine-producing cells in other parts of the brain) (Wolters, 2001). Most anti-Parkinsonian drugs (including levodopa, dopamine receptor agonists, dopamine release enhancers such as amantadine, and monoamine oxidase inhibitors such as selegiline) can cause psychotic symptoms.

Between 20 and 60% of people with Parkinson's disease develop psychotic symptoms (Kuzuhara, 2001; Wolters & Berendse, 2001). Hallucinations are more frequent than delusions in extrinsic cases (Aarsland et al, 1999) and visual hallucinations are more common than hallucinations in other sensory modalities (Hoeh et al, 2003). Epidemiological studies have found that the risk of psychotic symptoms in Parkinson's disease is higher in later stages of the disease and when there is concurrent dementia or depressive illness (Aarsland et al, 1999; Giladi et al, 2000).

Several open-label reports on the use of quetiapine in the elderly population, including patients with AD, DLB, and psychosis associated with Parkinson's disease, and are well summarized by Tariot and Ismail (2002). However, there has not been a published double-blind, placebo-controlled study with quetiapine in any of these populations. Studies of quetiapine in the elderly are limited only to case reports and open-label studies. However, the results of these studies indicate that quetiapine may be safe and effective in the treatment of psychotic disorders in the elderly and may have an added advantage in patients with Parkinson's disease because of its low EPS potential. Since there are no significant anticholinergic or cardiac effects, quetiapine may be an attractive choice in the elderly (Madhusudanan et al., 2001).

Pharmacological Treatment in PD

a) Antipsychotics

Treatment of psychotic symptoms in Parkinson's disease is difficult owing to older people's sensitivity to antipsychotics in general and to typical antipsychotics in particular. Clozapine has been the most widely used and studied anti-psychotic. Several double-blind controlled trials have established its efficacy. The optimal dose to reduce symptoms and minimize side-effects is 6.25-50 mg/day (Hoeh et al, 2003).

Clozapine is effective in treating drug-induced psychosis and prevented recurrence in PD and
allows for safe optimization of antiparkinsonian therapy. (Factor et al, 1992).

There have been several retrospective reports and open-label trials on other atypicals such as risperidone and olanzapine, but none has been shown to improve psychotic symptoms without worsening extrapyramidal symptoms (Ondo et al, 2002).

b) Cholinesterase inhibitors

There have been encouraging reports on the success of cholinesterase inhibitors such as donepezil and rivastigmine in improving both psychotic symptoms and cognitive deficits in Parkinson's disease (Bergman & Lerner, 2002; Bullock & Cameron, 2001; Fabbrini et al. 2002).

Should antipsychotics be used in dementia?

In addition to general concerns about the safety of neuroleptics for older people, the use of any medication to treat psychotic symptoms in dementia is increasingly being questioned. Do psychotic symptoms that are not distressing or adversely affecting the patient require treatment with medication (Kidder, 2003)? A careful assessment of potentially remediable environmental causes such as sensory deprivation, poor lighting and social isolation can prevent use of antipsychotics. Addressing other contributory and causal factors such as physical illness and side-effects of medication is equally important.

Medications that can cause psychotic symptoms in elderly people during use or on withdrawal are: Benzodiazepines, Antihistaminics (Cimeclidine), Anti-Parkinsonian drugs (Levodopa, Amantadine, Bromocriptine, Procyclidine), Anti-arrhythmics (Digoxin, Propranolol, Quinidine, Procainamide), Anti-inflammatory drugs (Aspirin, Indomethacin), Anticonvulsants (Phenytoin, Primidone, Carbamazepine), Steroids (Prednisolone), Anti-cancer drugs (Wood et al., 1988; Targum & Abbott, 1999; Targum, 2001).

II. Non-pharmacological treatment of psychotic symptoms in dementia

Non-pharmacological treatment of behavioural and psychological symptoms (including psychosis) in dementia has been the subject of increasing research in recent years. The non-pharmacological approach requires a detailed knowledge of the patient's personality and past psychiatric history, careful listening, observation of the current situation, and effective verbal and non-verbal communication.

The stages of a non-pharmacological approach to symptoms of dementia

Assessment

This includes systematic observation of the patient and should concentrate on the following areas:
• Identification of the problem through assessment of the symptoms
• Assessment of the interaction of symptoms with the environment by dividing them into antecedents and consequences
• Clarification of the negative effect of the symptoms, i.e. whether the patient and caregivers are negatively affected by them.

This area is important because psychotic symptoms that do not have a negative impact may not require treatment (Kidder, 2003).
Ascertaining possible causes for the symptoms

Some symptoms have environmental causes, and important areas to explore are:

- Whether the patient has a negative view of the caregiver
- Whether the patient is unable to understand the intentions of caregivers
- Whether the patient suffers from social isolation or sensory deprivation
- The patient's misinterpretations of the environment and situations.

Planning an intervention

The following points should be kept in mind:

- The intervention should be tailored to the needs of the particular patient and should address the cause of the symptoms
- The intervention may be directed at the patient, or at the environment, members of staff or the general system of care
- The need for regular assessment and re-evaluation of the intervention to monitor symptom improvement.

Reducing sensory deprivation

Practical measures aimed directly at the patient might include a hearing aid or glasses. External measures such as improving lighting, providing enhanced-contrasted materials, and larger type faces and objects may also help. An increase in positive stimulation through auditory sensations such as music and tactile sensations such as touch and massage may also prove useful.

Reducing inappropriate inner sensory stimulation

Simple practical measures can reduce stimulations that produce psychotic symptoms. Examples include removing mirrors if reflections cause the delusion of having phantom boarders in the house, or drawing a curtain over windows if the patient has a delusion of being spied on or followed.

Measures for specific symptoms

Misinterpretation of reality is the basis of a number of psychotic symptoms in dementia. A common symptom such as seeing caregivers as impostors can be addressed by training them to establish a positive relationship with the patient, introduce themselves with each encounter and clearly explain what they are going to do before doing it.

Delusions of infidelity or abandonment in institutionalized patients can be addressed by arranging frequent contact with their families. This can be real or simulated (by using videotapes of family members or stimulated presence therapy; Hall & Hare, 1997; Camberg et al., 1999). Measures such as frequent telephone calls and bringing familiar items from the patient's home can also be helpful in countering feelings of abandonment and betrayal.

The delusion that other people are stealing belongings can be addressed by providing duplicates of items that are easily mislaid (such as reading glasses), providing a remote control finder or using methods such retrieval, which teaches the patient always to return certain items to particular places.

C. BIPOLAR AFFECTIVE DISORDER (BPAD)

Post et al. (1982), Yassa et al. (1988), Dunn et al. (1996) have suggested that patients with
bipolar disorders constitute 5% to 19% of the elderly presenting for the treatment of mood disorders. The symptomatology of BPAD in elderly population is similar to their younger counterparts, however the response to treatment is incomplete (Van der Velda CD, 1970; Himmelhock et al. 1980) and chances of further recurrences and high mortality are also more (Shulman et al. 1993; Dhingra et al. 1991, Tohen et al. 1994).

The studies on geriatric bipolar disorder are very few and sparse. There are very few randomised controlled trials regarding the management of such patients, though the drugs used in young and adult bipolar population are widely prescribed in the elderly.

Elderly persons presenting with manic episodes represents minimum two groups. Firstly patients with recent onset illness and other group consisting of those with onset of illness in young adult life.

Review of Treatment modalities:

1. Lithium
2. Anticonvulsants
3. Antipsychotics
4. Benzodiazepenes
5. Combination treatment

1. Lithium (Li)

Most investigated drug in geriatric BPAD is lithium. Studies on its efficacy in pure geriatric patients are primarily retrospective. Most data comes from studies of mixed aged sample (Goodwin et al. 1990). The efficacy of lithium compared to chlorpromazine was found to be more in a study (Platman SR, 1970). In another study the results showed lack of sustained remission in elderly BPAD (Gildengers et al. 2005).

The exact relationship between the plasma lithium concentration and response is yet to be defined in elderly BPAD but Roose et al. 1979 and Schaffer et al. 1984) suggested that geriatric patients may respond to lower concentration (0.5 - 0.8 mEq/L) in comparison to the optimal lithium concentration (0.8 - 1.2 mEq/L) in mixed age group. Some other reports favor best response at conventional Lithium level when tolerated by geriatric patients (Young et al. 1992).

a) Neurocognitive Side Effects

These range from mild tremor to life threatening conditions such as delirium. It can dull cognitive performance (Judd et al. 1977), but this has not been examined in the elderly.

Neurological side effects like mental slowing, ataxia, tremor, cerebeller abnormalities were shown in several studies (Sajatovic et al. 2005; Murray et al. 1983 Chacko et al., 1987, Smith et al. 1982, Schaffer et al. 1984, Himmelhock et al., 1980).

Shulman et al. (2005) in a recent study showed that the incidence of hospitalization for delirium in patients of lithium was less than those on benztropine treatment but equivalent to those initiated in valproate.

b) Cardiovascular side effects

ECG abnormalities including sick sinus syndrome can occur in patient’s maintenance treatment.
at moderate lithium concentration (Roose et al., 1979).

Other side effects

Murray et al. (1983) and Hewick et al. (1977) reported renal side effects such as polyuria and polydipsia in more than 40% of elderly patients.

In a cross sectional study by Head et al. 1998 revealed that 32% of aged patients treated with Lithium developed hypothyroidism requiring thyroxine replacement therapy. In another study Shulman et al. (2005) reported need of Thyroxine prescription in 6% of elderly patients on lithium treatment which was twice that of elderly initiated on valproate.

Pharmacokinetic distortion in elderly BPAD patients that lead to increased lithium dose / concentration ratios put them at increased risk of side effects. Drug interactions of various drugs on lithium level in elderly. Thiazide diuretics, nonsteroids antiinflammatory agents, angiotensin converting enzyme inhibitors and sodium restriction can increase Lithium toxicity.

2. Anticonvulsants

There is no published study comparing valproate to lithium or to placebo in the elderly.


Chen et al (1999) retrospectively compared valproate with lithium and found comparable efficacy of the two agents in elderly BPAD patients. They also found that valproate concentration of 65-90 mg/ml were more effective than the blood levels of 45-66 mg/ml.

Regenold et al 2001 reported intravenous use of Valproate reaching concentrations of 44-87 mg/ml in blood and reduced psychopathology in 3 geriatric patients.

Greater efficacy was reported in manic elderly patients partially responsive to lithium, when valproate was added alongwith lithium (Goldberg et al (2000), Schneider et al (1998).

The combination therapy can also be useful in rapid cyclers as reported by Schneider et al (1998) and Sharma et al (1993).

Very limited studies have focused on antimanic effects of Carbamazepine. In a double blind comparison study of Carbamazepine and lithium revealed efficacy of both the drugs.

Sethi et al 2003 reported reduction in manic symptoms using Gabapentine in combination with antipsychotics or valproate in elderly. There are few case reports and case series where Oxcarbazepine and Topiramate were used. Though the role of new anticonvulsants is yet not established in geriatric practice.

3. Antipsychotics

There is little data regarding the efficacy of a typical antipsychotic medication in elderly BPAD patients.

The drugs studied for monotherapy or adjunctive therapy includes Risperidone, Olanzapine, Aripiprazole Quetiapine, Ziprasidone.

Risperidone & Olanzapine are most widely studies in mixed age BPAD patients as adjunct therapy

There are no studies establishing the relationship between the efficacy of these antipsychotics and their blood plasma concentration in elderly.

Side effects

Though FGAM's are well known to cause cognitive and neuromotor impairment in the elderly, some SGAM's (Clozapine, Olanzapine and Quetiapine) can also cause somnolence (Jeste et al 2005). On the other hand, risperidone and Olanzapine may enhance cognition in some elderly patients (Harvey et al 2003).

Elderly patients are more vulnerable than younger patients to the extra pyramidal side effects of antipsychotics, although they may experience acute dystonic reactions less often but their rate of akathesia may be equivalent to that seen in younger patients.


Benzodiazepines (BDZP’s)

BDZP’s have limited, adjunctive use in elderly BPAD patients (Young 2005).

Pomara et al 1998, Rickels et al 1987, Reidenberg et al 1978 reported that Benzodiazepines (BDZP’s) decreased memory consolidation, even short acting compounds can cause memory impairments. There is increased risk of falls and fractures (Sgadari et al 2000) along with disability (Sarkisian et al 2000) in elderly on long acting BDZP’s such as clonazepam.

II Continuation/Maintenance Treatment in BADP’s

As the natural course of illness is episodic, there is an increased need for continuation and maintenance pharmacotherapy but literature regarding the long term management of the elderly BPAD patients is even more limited than for acute management.

Information regarding long term treatment of elderly BPAD patients is primarily derived from naturalistic treatment in mixed age sample.

The number of psychiatric rehospitalization in patients on Li maintenance treatment was found comparable to those patients who were not on Li treatment.

Sajatovic et al. (2005) reported that Li delayed time to intervention for manic, hypomanic and mixed episodes. They also reported comparable results with lamotrigine.

The optimal duration of adjunctive agents like antipsychotics after successful treatment is not defined in elderly patients and there is no adequate information to guide mood stabilizer dosing in the context of continuation and maintenance treatment of BPAD patients (Young 2005).

Tondo et al. (2001) suggested the anti-suicide effect of Li in mixed aged patients. Muller et al. (2002)
showed increase risk of suicide in mixed aged BPAD patients but no similar research is available for elderly patients (Young 2005).

MODIFIERS OF TREATMENT

I. Age at onset and course of illness:

Overall toxicity of all the drugs is more in elderly.

The studies of Li treatment find greater over all side effects in elderly compared with younger patients (Smith et al. 1982, Roose et al. 1979, Murray et al. 1983) but Himmelhoch et al. 1980, Hewick et al. 1977 did not find any age effect.

Pattern of Carbamazepine cardio-toxicity may differ by age and sex (Kasarskis et al. 1992). He noted bradycardia and conduction delay without excessive drug exposure in elderly female.

Van der Velde (1970) noted poor acute benefit of Li in elderly compared with younger patients though no age effect was reported in mixed age manic patients on Li efficacy (Stokes et al. 1971) when compared with placebo.

Broadhead et al. (1990) reported increased incidence of cycling into a depressive episode during treatment of mania in elderly.

The effects on treatment outcome are not known in elderly BPAD and apparently no analysis address age effect on valproate and carbamazepine (Young 2005).

The effects of advanced age on long term treatment outcomes in various studies are conflicting, Vander Velde 1970 reported increased recurrence while Murray et al. (1983) reported increased psychopathology but not increased recurrence in BPAD elderly. Hewick et al. (1977) study was confounded by differing lithium concentration with age.

Modifiers of efficacy of Treatment

Young et al. (1997) reported no effect of age at onset on outcome at end point in elderly.

Schurhoff et al. (2000) did find differences in outcome of Li treatment in mixed aged BPAD patients.

DISCUSSION

Pharmacokinetic and pharmacodynamic changes of ageing: Age-related changes in the metabolism and physiology of the gastrointestinal, hepatic, renal and cardiovascular systems substantially alter drug distribution in the elderly. Collectively, they may result in a greater fraction of active, non-protein-bound drug than would occur if the same dose were given to a younger person. Age-related changes in liver enzyme levels are not uniform. In particular, no age-related changes were noted with the CYP2D6 iso-enzyme responsible for the metabolism of perphenazine, thioridazine and risperidone, although there is a possible age-related decline in function for the CYP3A4 iso-enzyme, the predominant metabolizer of quetiapine. A decline was also found with CYP1A2 iso-enzyme, a primary metabolizer of clozapine and olanzapine (Sweet & Pollock, 1998). As a result, different drug effects may occur, depending on the interactions and CYP system involved. Plasma concentrations of psychotropic drugs vary widely in patients receiving the same dosage. This variability is much greater in the elderly than in younger patients and makes generalizations about optimal dosages difficult on the basis of pharmacokinetic principles alone.
Age-related changes affecting the distribution of psychotropic drugs in the elderly:

- Delayed gastric emptying
- Reduced levels of plasma proteins, particularly albumin
- Reduced circulatory volume
- Decreased cerebrovascular perfusion
- Decreased synthesis and activity of hepatic microsomal enzymes
- Increased relative and absolute amount of adipose tissue
- Decreased body water
- Decreased renal blood flow
- Impaired glomerular filtration and reduced renal drug clearance

Established mood stabilizers

Risk of Mania decline in late life, nonetheless mania and hypomania affect 5-10% of psychiatric patients. The following are the established mood stabilizers:

- Lithium salts
- Valproate
- Carbamazepine

“Putative Mood stabilizers” Newer Anticonvulsant

- L-Thyroxine
- Phosphatidyl choline
- Progesterone
- Clozapine
- Olanzapine
- Magnesium salt

LITHIUM

1. Lithium: Most investigated drugs in geriatric mania - less effective when mania is co morbid with neurological and medical disorders. Less effective in patients with psychotic symptoms
2. High plasma levels may reach even in low dosage because of decreased renal clearance.
3. Dosage- Introduce slowly starting with daily dosage of 150 mg and about one half of the dosage required for young adult is sufficient for elderly
4. T½ = Half life is about 24-36 hours in patients in 70s therefore steady state pharmacokinetics are anticipated 5 or more days after the stabilization of daily dosage.
5. Lithium plasma level of 0.3 to 0.6 meq/L is found to be effective.
6. Negative effect seems to correlate proportionally with dose of blood concentration of lithium.
7. Whether lithium response diminished with age is still a controversy. Some noted a loss of efficacy while other has doubted this.

Common side effect of lithium

Neurological - Mental slowing, ataxia, tremor, cerebellar abnormalities
Renal- Urinary frequency, renal failure (rare)
Cardiac (all more common in elderly) - Sinus node dysfunction, sinoatrial block, bundle branch block, ventricular arrhythmia, myocardial injury.

Endocrine- Nontoxic goiter (10%), increase in fasting blood glucose

Gastro intestinal - Dose related nausea, gastric irritation, diarrhea, significant weight gain.

Dermatologic - Possible worsening of a number of chronic skin conditions including Psoriasis.

Others - Arthritis, Peripheral edema

Many of the side effects listed in above table are common complaints in the elderly. Elderly patients with benign prostatic hypertrophy or difficulty ambulating at night because they use a walker may not tolerate the nocturia and cerebellar dysfunction frequently associated with lithium therapy.

Lithium can worsen cognitive problem in elderly. Lithium associated weight gain and increase in fasting blood glucose levels can worsen adult onset diabetes mellitus.

- Sinus node dysfunction and prolonged cardiac conduction can be made clinically significant by lithium addition.
- Chronic psoriasis and peripheral edema can be exacerbated by lithium therapy.
- Lithium can worsen arthritis.

**Drug interaction with lithium**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect of lithium</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>↑ lithium level</td>
<td>Avoid this combination or Reduce dosage, monitor Lithium level</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>↑ or ↓ lithium level</td>
<td>Avoid this combination or Alter either dosage, Monitor lithium level</td>
</tr>
<tr>
<td>Potassium sparing Diuretics</td>
<td>↓ Lithium level</td>
<td>Monitor lithium level and adjust dosage</td>
</tr>
<tr>
<td>Nonsteroidal anti-Inflammatory drugs</td>
<td>↑ Lithium level</td>
<td>Use lower dosage of lithium; consider aspirin or sulindac</td>
</tr>
<tr>
<td>Angiotensin-converting Enzyme inhibitors</td>
<td>↑ lithium level, toxicity reported</td>
<td>Use lower dosage of lithium, monitor lithium level</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>↑ or ↓ lithium level</td>
<td>Monitor lithium level Closely</td>
</tr>
</tbody>
</table>
Sodium Valproate and Carbamazepine

**Subtype of patients with mania who are responsive to anticonvulsants**

- Dysphoric mania and severe psychosis
- No family history of affective illness
- Older age
- Mania associated with neurological dysfunction
- Rapid cycling mania
- Lithium-non responsive mania

Anticonvulsant appears to be effective in both lithium responders and lithium non-responders.

**Sodium valproate**

It is more effective than lithium in rapidly cycling manic patients and in those with dysphoric mania. Mania with co morbidity neurological brain disease may be more responsible to valproate. Dosage as low as 250 mg/day appears to result in adequate mood stabilization but many more patients will not achieve adequate serum level with dosage below 750 mg/day.

**Carbamazepine**

Patients with dysphoric mania, rapid cycling mania, lithium non-responsiveness and no family history of affective illness have increased response to carbamazepine. Carbamazepine therapy is initiated at 100 mg twice daily and increased to 200 mg twice daily over 3-4 days as tolerated. Dosage are adjusted (usually 400 to 800 mg/day) to obtain a blood level of 6 to 12 mg/ml. Because of auto-induction phenomena further increase in dosage will need to be made over the first 2 to 3 weeks of treatment to maintain a steady-state concentration.

**Side effects of valproic acid and carbamazepine (William M., McDonald J., 2000)**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
</tr>
<tr>
<td>Dose-related drowsiness and ataxia</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td>Fine resting tremor</td>
<td>VPA &gt; CBZ</td>
</tr>
<tr>
<td>Horizontal nystagmus, diplopia, blurred vision</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Insignificant and transient elevation in liver transaminases</td>
<td>VPA &gt; CBZ</td>
</tr>
<tr>
<td>Hepatotoxicity (rare)</td>
<td>VPA &gt; CBZ</td>
</tr>
<tr>
<td>Pancreatitis (rare)</td>
<td>VPA &gt; CBZ</td>
</tr>
<tr>
<td><strong>Hematopoietic</strong></td>
<td></td>
</tr>
<tr>
<td>Transient leucopenia</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>VPA &gt; CBZ</td>
</tr>
<tr>
<td>Agranulocytosis (rare)</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
</tr>
<tr>
<td>Benign skin rashes</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td>Exfoliative dermatitis (rare, potentially fatal)</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td>Stevens Johnson syndrome (rare, potentially fatal)</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td>Lyell's syndrome (rare, potentially fatal)</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>VPA</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>VPA</td>
</tr>
<tr>
<td>Transient hair loss</td>
<td>VPA</td>
</tr>
<tr>
<td>Anticholinergic side effect</td>
<td>CBZ</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia secondary to SIADH</td>
<td>CBZ &gt; VPA</td>
</tr>
<tr>
<td>Weight gain due to decrease free thyroid hormone</td>
<td>CBZ</td>
</tr>
</tbody>
</table>

(30)
**Drug interactions with Valproic Acid**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Increased phenobarbital level</td>
<td>Reduce dosage</td>
</tr>
<tr>
<td>Magnesium- and aluminium containing antacids</td>
<td>Increased valproic acid level</td>
<td>Monitor valproic acid level; reduce dosage</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Decreased valproic acid level; possible increased carbamazepine level</td>
<td>Monitor valproic acid level; adjust dosage</td>
</tr>
<tr>
<td>Aspirin and naproxen</td>
<td>Increased valproic acid level</td>
<td>Avoid salicylates or other drugs bound to plasma albumin</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Increased sedation</td>
<td>Use with caution</td>
</tr>
</tbody>
</table>

**Dose adjustment**
- Increases VPA level: Aspirin, erythromycin, fluoxetine
- Increases CBZ levels: Erythromycin, calcium-channel blockers, cimetidine, terfenadine, verapamil, (elevation in the toxic epoxide metabolite of CBZ when VPA is added to CBZ).
- CBZ decreases the serum concentrations of a number of medications via induction of cytochrome P450 enzymes in the liver: Premarin, caumadin, theophylline, steroids, vitamin K, quinidine, tricyclic antidepressants, narcoleptics, and benzodiazepines.

**Common side effects**
- Neurological: Dose-related drowsiness and ataxia (CBZ > VPA), fine resting tremor (VPA > CBZ), horizontal nystagmus.
- Gastrointestinal: VPA is associated with nausea which can be lessened by taking with meals or using enteric-coated divalproex sodium. Insignificant and transient elevation in liver transaminases; patients should be monitored for evidence of hepatotoxicity (anorexia, nausea, jaundice, malaise, abdominal pain and bruising).
- Hematopoetic: Transient leucopenia (CBZ > VPA) or thrombo-cytopenia (VPA). Patients should be monitored carefully in the first 6 months of therapy for infection, easy bruising, or bleeding.
- Dermatologic: Benign skin rashes.
- Other: Weight gain and transient hair loss (VPA), anticholinergic side effects (CBZ).

**Rare idiosyncratic reactions:**
- Renal: Renal failure.
- Gastrointestinal: Hepatotoxicity (V PA > CBZ), pancreatitis.
- Hematopoetic manifestations: Aplastic anaemia, (CBZ > VPA), thrombocytopenia with platelets < 50,000 (V PA > CBZ); may be more common in the elderly.
- Dermatologic: Potentially fatal reactions including exfoliative dermatitis, Stevens-Johnson
syndrome, Lyell syndrome.

- Endocrine: Hyponatremia secondary to SIADH (CBZ), weight gain due to decrease in free thyroid hormone (CBZ).
- Endocrine: Hyponatremia secondary to SIADH (CBZ), weight gain due to decrease in free thyroid hormone (CBZ).

- **CARDIOVASCULAR ILLNESS**

  **Lithium**
  - Although propranolol is used in controlling lithium tremor, combination may aggravate bradycardia and precipitate bradyarrhythmias. Verapamil also produces the same.
  - Diltiazem may decrease serum lithium levels, so readjustment is needed to achieve therapeutic serum lithium level.
  - ACE inhibitors and Thiazides increase serum lithium levels.
  - Bronchodilator increases lithium excretion.
  - T-Wave flattening or inversion may occur in 30-100% patients.
  - Common conduction defects in sinus nodes dysfunction especially in vulnerable patients.

  **Carbamazepine**
  - Decrease plasma level of beta blocker.
  - Diltiazem/verapamil increases plasma level CBZ.
  - Enhances metabolism of warfarin. (Decreased PT ratio).
  - Elevation of total cholesterol.
  - CBZ - Lithium combination may produce sinus node dysfunction

  **Valproate**
  Combination with warfarin produces displacement of protein binding of warfarin increased PT ratio.

- **RENAL DISORDERS**

  **Lithium**
  - Nephrogenic diabetes insipidus in 20-70%.
  - Lithium does not produce permanent renal damage leading to renal failure.
  - Contraindicated in acute renal failure, increased risk in patients with preexisting glomerulonephritis, pyelonephritis, tubulointerstitial disease, renal condition producing acidosis or acidification defects.
  - Progressively decreasing creatinine clearance necessitates lithium stoppage.

  **Carbamazepine**
  Anticholinergic effect, rarely acute renal failure.

  **Valproate**
  No renal problems.

- **HEPATIC DISORDERS**

  **Lithium**

(32)
No problems CBZ
May produce hepatic dysfunction hepatocellular failure and cholestatic jaundice reported VPA
- Contraindicated in liver dysfunction
- Stop drug in transaminase increase
- Pancreatitis, cholecystitis

• RESPIRATORY DISORDERS

Lithium
- Bronchodilators increases lithium excretion.
- Lithium used in COPD may precipitate hypercapnia.

CBZ
- Decrease theophylline level due to enzyme induction.
- Theophylline decrease CBZ levels by 50%.
- Isoniazide decrease and plasma level of CBZ by 45%.

Valproate
Isoniazide increases plasma Valproate levels due to inhibited metabolism.

• THYROID DISORDERS

Lithium
- Chemical hypothyroidism in 50%.
- Diffuse non tender goiter without hypothyroidism (6%).
- Clinical hypothyroidism 3-4%.
- Preexisting hypothyroidism is not an absolute contradiction to lithium
- Chemical hypothyroidism may be requiring thyroid supplements.

CBZ
Decrease plasma level of thyroid hormone due to enzyme induction.

• DIABETES

Lithium
- Increased, decreased or unchanged glucose tolerance, weight gain (30%)

VPA
- Weight gain (upto 59%) more in female, PCOD syndrome, False positive Ketone results.

Carbamazepine
May produce weight gain

• METABOLIC DISORDER
- CBZ may cause SIADH especially in elderly (1-12%).
- Excessive loss of sodium increases lithium levels.
- Heavy sweating leads to reduce levels of lithium.

### ARTHRITIS
- NSAIDS especially piroxicam and indomethacin increase lithium effect (12-66%).
- CBZ may precipitate systemic lupus erythematosus.
- CBZ may reduce plasma levels of corticosteroids.
- Combination of salicylate with VPA displaces VPA from protein binding and decrease clearance with 4 fold VPA levels.

### HEMATOLOGICAL DISORDERS

**Lithium - Leucocytosis.**

**VPA - Reversible thrombocytopenia with high dose macrocytic anemia, rarely.**

**CBZ - Aplastic anemia, thrombocytopenia agranulocytosis.**

### INFECTIOUS DISORDERS
- Metronidazole - decrease renal clearance of lithium. Increase plasma level of CBZ.
- Erythromycin - Increase plasma VPA levels.
- Clarithromycin - Increases plasma CBZ levels.
- Doxycycline - levels decreased if combined with CBZ.
- Ampicillin, tetracyclin, doxycycline, spectinomycin produce decreased renal clearance of lithium.
- Combined use of VPA with zidovudine - increased level of zidovudine (38%).
- Acyclovir decreases VPA levels.
- CBZ decreases plasma cyclosporine levels.
- CBZ levels are increased when used with antifungal (Ketoconazole)

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Lithium</th>
<th>CBZ</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Renal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Diabetes</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatic</td>
<td>✓ ✓ ✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hematological</td>
<td>✓ ✓ ✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Thyroid</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Arthritis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Infectious</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Metabolic</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓-Bad, ✓-mederate, ✓✓-Good
NEWER ANTICONVULSANT

Newer anticonvulsants (Gabapentin, Lamotrigine, Topiramate) are potential alternatives to lithium, antipsychotic, valproic acid and CBZ in patients who fail initial therapy with the traditional agents. However there are no clinical trials in the elderly and it is too early to determine the role of these newer drugs in the treatment of geriatric mania.

GABAPENTIN

At present there are inadequate data to support the use of gabapentin as either monotherapy or adjunctive therapy in mania, except as a 3rd and 4th line treatment. The initial dose is usually 300 mg with dosage increases every 3 to 7 days as tolerated, up to a maximum of 900 to 2400 mg/day. It may be useful in geriatric agitation and anxiety state.

Lamotrigine

- In general has a benign side effect profile including dizziness, headaches and diplopia.
- Associated with cutaneous rash (in up to 10%) that may evolve into toxic epidermic necrolysis.
- May be a useful adjunctive medication when added to lithium or valporate in depressed or patients with rapid cycling mania.
- Dosing is starting dose of 25 mg/day with dose titration of no more than 25 mg/week and maintenance dose of 25 to 250 mg/day.
- No published study of the use of lamotrigine in elderly bipolar patients.
- Lamotrigine is not recommended as a first line treatment in this population.

Topiramate

- Majority of side effects associated with topiramate are mild or transient in nature.
- Less common side effect includes kidney stone and depression.
- Unique side effect compared with antidepressant and lithium is weight loss, and advantage in improving compliance.

Treatment of Psychotic agitation in the elderly

Patients who are psychotic and agitated are treated acutely with a combination of antipsychotics and benzodiazepine, after they are stabilized over first 24 to 48 hours, the anticonvulsants medication is started and the antipsychotics and benzodiazepine are tapered over a period of 5 days.

Recommended doses of atypical anti-psychotics for elderly people

<table>
<thead>
<tr>
<th></th>
<th>Starting dose (mg/day)</th>
<th>Maximum dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>6.25</td>
<td>50-100</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25-0.5</td>
<td>2-3</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1-5</td>
<td>5-15</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5-25</td>
<td>100-200</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>15-20</td>
<td>80-160</td>
</tr>
</tbody>
</table>
### Potency and side-effects of traditional neuroleptics

<table>
<thead>
<tr>
<th>Potency</th>
<th>Sedation</th>
<th>Hypotension</th>
<th>Anticholinergic effects</th>
<th>Extrapyramidal side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlormpromazine</td>
<td>High</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Initial treatment**
- Haloperidol 0.25-0.5 mg intramuscularly or orally.
- After one hour, administer lorazepam 0.5 mg intramuscularly or orally.
- Stabilization
- Repeat alternating doses every hour until calm
- Monitor carefully to avoid over sedation
- Alternative regimen if extra pyramidal symptoms develop
- Atypical antipsychotics, risperidone (0.5 mg), or olanzapine (2.5 to 5.0 mg), or less potent neuroleptics, thiothixine (2 mg), or molindone (10 mg)
- Avoid chlorpromazine and thioridazine due to their anticholinergic and hypotensive side effect.

**Chronic medication**
Daily dose of medication is determined by adding the total dose of each medication required to calm the patient and dividing it equally throughout the day.

Adjunctive antipsychotic medication
Common antipsychotic drug interactions in the elderly

<table>
<thead>
<tr>
<th>Combination</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs and conventional antipsychotics</td>
<td>Raises blood antidepressant concentrations</td>
</tr>
<tr>
<td>SSRIs and clozapine</td>
<td>Raises blood clozapine concentrations</td>
</tr>
<tr>
<td>Risperidone and clozapine</td>
<td>Raises blood clozapine concentrations</td>
</tr>
<tr>
<td>Smoking</td>
<td>Lowers blood antipsychotic concentrations</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Lowers blood antipsychotic concentrations</td>
</tr>
<tr>
<td>Anticholinergic drugs</td>
<td>Additive memory and delirious effects</td>
</tr>
<tr>
<td>Anticonvulsant, antihypertensive</td>
<td>Additive sedative and delirious effects</td>
</tr>
<tr>
<td>and sedative drugs</td>
<td></td>
</tr>
</tbody>
</table>

TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors.

Side-effect profile of available antipsychotic drugs (from Maximer et al, 1999)

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Neuroleptics</th>
<th>Clozapine</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>± to +++</td>
<td>+++</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>EPS</td>
<td>± to +++</td>
<td>0 to ±</td>
<td>0 to ±</td>
<td>0 to ±</td>
<td>0 to ±</td>
</tr>
<tr>
<td>Orthostatic</td>
<td>+ to +++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+ to ++</td>
</tr>
<tr>
<td>hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>++ to +++</td>
<td>0</td>
<td>++</td>
<td>0 to ±</td>
<td>0 to ±</td>
</tr>
<tr>
<td>elevation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>+ to +++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+ to ++</td>
</tr>
<tr>
<td>Seizures</td>
<td>± to ++</td>
<td>++</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+ to ++</td>
<td>+++</td>
<td>++</td>
<td>++ to +++</td>
<td>++</td>
</tr>
</tbody>
</table>

0, absent; ±, minimal; +, mild; ++, moderate; ++++, severe; EPS, extrapyrimidal side-effects.

The Pfizer study 054 for ziprasidone (OHRMS, 2001) made some interesting comparisons between antipsychotics and persuaded the FDA that any increase in QT interval is unlikely to be clinically significant.

Mean increases in QTc for various antipsychotic drugs (CI 5-6 ms)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Change in QTc (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>300</td>
<td>36</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>160</td>
<td>20</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>800</td>
<td>14.5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>16</td>
<td>11.6</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20</td>
<td>6.8</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>15</td>
<td>4.7</td>
</tr>
</tbody>
</table>
Risperidone

- Risperidone has the most robust evidence in terms of efficacy for treatment of behavioral and psychological symptoms in dementia. It seems to be well tolerated, although its receptor profile suggests a greater tendency to cause extra pyramidal side-effects (EPS).
- Daily divided doses of 0.5 to 3 mg
- Monitor patient carefully for orthostatic hypotension and EPS as dose is increased

Olanzapine

- The advantages of olanzapine in the elderly include a good effect on positive and negative psychiatric symptoms and a low incidence of EPS. The potential for anticholinergic effects remains a concern.
- Daily doses of 2.5 to 10 mg/day.
- Most common side effect are sedation (usually given at hour of sleep). Transient elevation in liver enzyme have been reported.

Risperidone plus olanzapine

Observe for increased agitation or other manic symptom because of breakthrough mania with risperidone.

Clozapine

- Clozapine is poorly tolerated in the elderly; there is an age-related increase in risk of agranulocytosis; rapid titration is particularly problematic. It should be reserved for patients who are intolerant of risperidone and olanzapine, yet require adjunctive medication and cannot be placed on a traditional neuroleptic (patients with tardive dyskinesia or co-morbid Parkinson’s disease).
- Daily doses start at 12.5 mg, increase to 50 mg.
- Usually given at hour of sleep, but can be divided during the day if patients is not too sedated.
- Patients with a history of a seizure disorder should be maintained on an anticonvulsant (CBZ and clozapine usually not given together because of the increased incidence of leucopenia).
- Monitor for orthostatic hypotension and weekly complete blood count to assess for evidence of bone marrow toxicity.

Quetiapine

Quetiapine is theoretically least likely to cause EPS, suggesting it as the drug of choice for Parkinson’s disease with psychosis and dementia with Lewy bodies.

Patients on neuroleptic medication should be gradually tapered off the medication after stabilization on lithium or anticonvulsant. Patients who cannot be tapered over a period of 4 to 6 weeks without breakthrough psychotic episodes or who cannot tolerate the neuroleptics or develop significant side effect (including tardive dyskinesia) should be considered for treatment with an atypical antipsychotic.

RECOMMENDATIONS:

There are several key points to be remembered about antipsychotic medications in elderly. Antipsychotic drugs are indicated for treating psychotic disorders, including schizophrenia, delusional disorder, psychotic symptoms in mood disorders, and for a number of organic psychoses. Antipsychotics remain the only established mode of pharmacotherapy for behavioral and psychological...
symptoms in dementia, although their efficacy here is modest. The elderly are more sensitive to the side-effects of psychotropic and non-psychotropic medication owing to age-related pharmacodynamic and pharmacokinetic changes, higher rates of physical co morbidity and polypharmacy. Conventional antipsychotics carry a high risk of causing extra pyramidal side-effects and tardive dyskinesia in the elderly population.

Initiating Anticonvulsant therapy

Initiating therapy

- Base line ECG, CBC with platelet, biochemistry profile with liver enzymes
- Valproic acid: Elderly patients are started on 250 mg at hour of sleep and increased to 250 mg bid over 3 to 5 days as tolerated. Dosages are adjusted (usually between 500 to 1000 mg/day) to obtain a blood level between 60 to 100 mcg/ml
- Carbamazepine: CBZ is started at 100 mg bid and increased to 20mg bid over 3 to 5 days as tolerated. Dosage are adjusted (usually 400 to 800 mg/day) to obtain a blood level to 6 to 12 mcg/mL. Because CBZ induced liver enzymes which increase the metabolism of CBZ (auto induction), further increases in CBZ need to be made over the first 2 to 3 weeks of treatment to maintain a steady serum concentration.

Initiating and monitoring lithium therapy

Initiating therapy

- Pretreatment laboratory evaluation: Electrocardiogram, electrolytes, fasting blood glucose, and thyroid stimulating hormone

Initial dosage

- Lithium carbonate 300 mg at hour of sleep

Dosage adjustment

- Check blood levels in 3 days; adjust dosage to maintain a serum level from 0.6 to 1.0meq/L, depending on clinical response
- Elderly patients often require 300 to 900 mg/day of lithium carbonate to maintain an adequate clinical response
- Renal clearance of lithium may be altered by nonsteroidal anti-inflammatory agents and thiazide diuretics.

Management of psychoses in elderly poses a special problem because of the fact that certain disorders predominantly occurring exclusively in elderly e.g. dementia, vascular brain pathology and associated psychoses, psychoses associated with Alzheimer's dementia need careful evaluation on one hand and due to compromised metabolic state, determination of dose of antipsychotic need careful precise monitoring and decision making on the other hand. Non pharmacological management especially psychosocial support by care givers also determine the course and outcome of the illness, and ways in which they can handle the special symptoms like aggression, suicidality and restlessness in elderly needs to be given attention so that pharmacological treatment can also be accordingly decided. In the absence of psychosocial support and poor understanding of these symptoms, likelihood of increase in doses of antipsychotic may by an unwanted decision. Therefore managing psychoses in elderly requires clinical skills of
evaluation in emergency setting, managing emotions of care givers, handling with their attitude and creating the support system at the same time. Following algorithm is suggested for diagnosis and management:

**PSYCHOSES IN ELDERLY - ALGORITHM OF TREATMENT**

1. **Psychoses**
   - With disorientation and changes in consciousness
     - YES → Delirium
     - NO → Detailed history and clinical evaluation, Rule out physical causes.
     - Routine Lab investigation

2. **Primarily psychoses**
   - Memory loss precedes psychoses
     - NO → Psychoses secondary to dementia/OBS
     - YES → Neuro-evaluation, Imaging studies

3. **H/o polarity with intervals/ Rapid cycling**
   - YES → BPAD
   - NO → Choice of antipsychotic based on:
     - Lab investigations
     - Informed consent of patient and / or care givers
     - Start atypical antipsychotic drugs.

4. **Go slow and low, titrate if necessary, to minimum effective dose.**
   - Adjust according to tolerability and response.
   - Sedative / Benzodiazepine if needed.
   - Assess over 6 to 8 weeks.

5. **Poor compliance**
   - Change drug and follow above process
   - Consider use of atypical and/or typical drugs.

6. **Poor tolerability**
   - Change the drug
   - Psychosocial therapies & support crucial in all phases of treatment
   - If poor compliance related to other factors, investigate social and psychological factors.
   - Provide appropriate support and/or therapy.
   - Repeat above process.

**Note:**
- Dose of antipsychotic in elderly is approximately half of adult dose.
- Dose of antipsychotic in elderly dementic is further reduced to approximately half of that used in severe mental illness in elderly.
- Refractory cases try combination of clozapine + Amisulpride.
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