Chapter 1

Introduction & Literature Review

Increased life expectancy and a falling birth rate have increased the number of elderly people worldwide. Since the prevalence of dementia doubles every 5 years after the age of 60 (Jorm, 1987), a rapidly expanding elderly population has led to a boom in the number of people with dementia. Hong Kong is no exception to this trend. There has been a significant rise in the number of dementia patients locally in the past decade. As reported in a recent study, the weighted prevalence of dementia among Chinese elderly in Hong Kong was as high as 6.1% (Chiu *et al.*, 1998).

In the course of dementia research, cognitive symptoms of dementia have been the most widely studied (Cohen-Mansfield, 1986; Fairburn, 1998). Recent years have seen the growth of research interest in behavioural and psychological symptoms of dementia (BPSD). BPSD are defined as 'symptoms of disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia' (Finkel *et al.*, 1996). Such emergence of recognition is partly due to the high prevalence of BPSD in those with dementia. A longitudinal study of the course of BPSD showed that 64% of patients with Alzheimer's disease (AD) had one or more BPSD at initial evaluation (Devenand *et al.*, 1997). It echoed earlier findings by investigators like

Swearer *et al.*, (1988) who revealed that 80% of dementia patients had one or more behavioural disturbances during the course of their illness.

Another reason for the growing concern for BPSD in the 1990s is that they present severe problems to patients, their families and caregivers, and society at large. BPSD can result in suffering, premature institutionalization, increased cost of care, and significant loss of quality-of-life not only for the patients (Finkel *et al.*, 1996) but also their families and caregivers (Donaldson *et al.*, 1997).

Nevertheless, BPSD are treatable and are more amenable to therapy than other symptoms or syndromes of dementia. It stimulated the emergence of a substantial number of drug trials aiming at BPSD alleviation. Of the different pharmacological agents used in the management of BPSD, antipsychotics are the best-documented (American Psychiatric Association, 1997).

Conventional antipsychotics have traditionally been prescribed for behaviourally disturbed dementia patients. Results of a meta-ananlysis of controlled trials of antipsychotic treatment in dementia indicated that antipsychotics were significantly more effective than placebo (Schneider *et al.*, 1990). Based on the evidence, the symptoms that appear to be most responsive to antipsychotic medication are hallucinations, delusions, hostility, physical aggression and violent behaviours

(Barnes *et al.*, 1982; Petrie *et al.*, 1982; Devenard *et al.*, 1989).

While these data consistently support the modest efficacy of conventional antipsychotics, their use in demented elderly has been restricted by their potentially serious side effects. High-potency agents (e.g. haloperidol, fluphenazine) are most strongly associated with akathisia and parkinsonian symptoms whereas low-potency agents (e.g. thioridazine, chlorpromazine) are associated with sedation, confusion, delirium, postural hypotension, and anticholinergic side effects. Age and disease-related changes in pharmacokinetic and pharmacodynamic properties of the prescribed drugs has rendered dementia patients more sensitive to side effects of antipsychotic medications. In addition to these common side effects, antipsychotic medications are associated with an increased risk of tardive dyskinesia, which is more likely with increasing dose and duration of treatment and occurs more commonly in women, demented individuals, and the older adults in general. The risk may be as high as 30% for elderly patients with significant exposure (Jeste *et al.*, 1995). Furthermore, the use of anticholinergic agents (e.g. benzhexol) to relieve extrapyramidal symptoms (EPS) can block already depleted acetylcholine and results in undesirable conditions like delirium and worsening of cognitive impairment.

Novel antipsychotics offer significant theoretical advantages over conventional ones because of a reduced potential to cause EPS in the older adults, the most vulnerable

population. The 5-HT_{2A} antagonism produced by the novel antipsychotics may be responsible for their lower propensity to induce EPS. In view of their better tolerability, it is suggested that novel antipsychotics may be particularly useful in treating demented elderly.

Case studies of dementia patients suggest that risperidone, one of the novel antipsychotics, is useful in alleviating BPSD (Madhusoodanan *et al.*, 1995; Jeanblanc *et al.*, 1995). Risperidone, a benzisozaxole derivative, is a potent centrally acting combined serotonin-5HT_{2A} and dopamine-D_2 receptor blocker (Stahl, 1999). It also antagonizes alpha-2 and alpha-1 adrenoceptors and histamine-H1 receptors. On the contrary, risperidone does not bind to muscarinic cholinergic receptors. It is associated with low EPS potential and minimal anticholinergic side effects and has made risperidone an attractive choice in the management of behavioural and psychological symptoms associated with dementia.

However, there is a paucity of data from controlled trials of risperidone in dementia. Most of the published literature comprises nonblind trials, case reports and retrospective chart reviews. In a retrospective study of 186 demented elderly, Frenchman *et al.* (1997) concluded that safe, effective doses were readily achieved with risperidone but difficult to achieve with haloperidol or thioridazine because their effective doses often caused unacceptable side effects, notably EPS.

In the nonblind trials in elderly patients with dementia, risperidone was effective in reducing agitation and psychotic symptoms. Goldberg and Goldberg (1997) reported favourable results in 109 nursing home residents with dementia-related disturbed behaviour treated with low doses of risperidone for 6 months. In this nonblind trial, risperidone was well tolerated and effective, especially for agitation, verbal outbursts, aggressiveness, depression, anxiety and sleeping problems. Risperidone was very helpful in 38%, moderately helpful in 26%, slightly helpful in 17% and was not helpful in 19% of patients. Similar findings were reported in another open-label study by Jeste *et al.* (1996), in which marked improvement was noted in 43% of patients treated with risperidone and no serious adverse event was recorded.

To date only 1 large controlled trial of risperidone in the treatment of behavioural symptoms of dementia has been published. In this study, 625 patients with dementia were randomly assigned to receive placebo or 0.5mg/day, 1mg/day, or 2mg/day of risperidone for 12 weeks. Symptoms significantly reduced in patients receiving 1 or 2mg/day of risperidone. Risperidone was generally well tolerated even though more adverse events were reported by patients receiving 2mg/day of risperidone than by patients receiving 1mg/day. The frequency of EPS in patients receiving 1mg/day of risperidone was, however, not significantly greater than in placebo patients.

While data indicate that risperidone may be the drug of choice, comparative studies

assessing the efficacy and tolerability of conventional and novel antipsychotics in patients with BPSD are still warranted. Besides, as Katz's trial adopted a fixed dosing regimen, a flexible dosing design may help us to clarify the optimal dose required in dementia patients. Furthermore, this randomized double-blind trial also aims at verifying the use of risperidone and haloperidol in the Chinese population.