The Older Patient: The Ongoing Challenge of Efficacy and Tolerability

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The clinical management of older schizophrenic patients presents particular clinical challenges. Antipsychotics are among the most widely prescribed class of medications for elderly patients. However, the increased frequency of chronic illnesses and thus the potential need for polypharmacy means that the most appropriate treatment strategy for the older schizophrenic patient is not easily extrapolated from the wealth of clinical trials conducted in younger patients. The development of atypical antipsychotics, with their lower propensity to cause adverse effects and cognitive impairment, offers considerable potential benefits to the older schizophrenic patient. The particular problems and key issues that should be addressed when selecting an appropriate antipsychotic for schizophrenic patients in this sensitive population, as well as the place of the new atypical antipsychotic agents in treating this population, are discussed. *(J Clin Psychiatry 1999;60[suppl 23]:29–33)*

The proper management of older schizophrenic patients presents particular clinical challenges to clinicians. As the population as a whole continues to age, so will the proportion of older schizophrenic patients clinicians are likely to see in practice increase.

The frequency of chronic illness increases with age, as does the potential for polypharmacy. These facts, combined with natural age-related changes in a range of metabolic processes, mean that the selection of appropriate treatments requires careful consideration and regular review. Older patients are particularly sensitive to a variety of side effects of drug treatment, which can contribute to both treatment intolerance and noncompliance. In addition, the elderly exhibit considerable heterogeneity, but they are usually considered as a single clinical population despite the fact that chronological age does not necessarily correlate with biological age and that the health status of the elderly varies considerably from frail and ill to fit and healthy. For all these reasons, the most appropriate treatment strategy for the older schizophrenic patient is not easily extrapolated from the wealth of clinical trials conducted in younger patients.

Conventional antipsychotic agents, owing to their association with a range of side effects, have proved less than ideal for the treatment of schizophrenia in older patients. The development of atypical antipsychotics, including quetiapine, with its lower propensity to cause adverse effects such as extrapyramidal symptoms (EPS) and cognitive impairment, offers considerable potential benefits to the older schizophrenic patient. This article discusses particular problems and key issues that should be addressed when selecting an appropriate antipsychotic for schizophrenic patients in this sensitive population as well as the potential role of the newest atypical antipsychotic, quetiapine, in treating this population.

ANTIPSYCHOTICS AND THE OLDER SCHIZOPHRENIC PATIENT

Antipsychotic agents are among the most widely prescribed class of medications for elderly patients, yet the treatment of older schizophrenic patients is based largely on clinical research and experience with younger patients and empirical experience in older patients.

Conventional antipsychotics are generally effective in the relief of the positive symptoms of schizophrenia such as hallucinations and delusions. However, they have relatively little effect on negative symptoms such as emotional withdrawal and impaired attention. In contrast, atypical antipsychotics, including clozapine, risperidone, olanzapine, and quetiapine, are effective in the relief of both the positive and negative symptoms of schizophrenia. Some data suggest that they may confer a modest, but significant, benefit in terms of cognitive function (see Velligan and Miller,[1] this supplement), which may be particularly important in elderly patients. There is a lack of controlled, randomized clinical trials comparing the efficacy of conventional and atypical antipsychotics in older schizophrenic patients, and the available studies have tended to

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be open and/or non–placebo controlled or to have recruited patients with widely varying psychotic disorders. Nevertheless, there is good evidence to support the efficacy of atypical antipsychotics in elderly schizophrenic patients,[2] and, as a group, these agents appear to be at least as effective as the conventional agents. In the absence of unequivocal data to support an efficacy benefit of one class of antipsychotics over the other, the incidence and severity of side effects and the overall tolerability of individual agents are a rational guide to the selection of an appropriate treatment.

The use of conventional antipsychotics in elderly patients is limited by the association of these agents with a range of side effects, including EPS and added toxicity due to the frequent requirement of concomitant anticholinergic medication to control the EPS. Atypical antipsychotics are associated with lower overall rates of EPS, which may make them particularly well suited for the treatment of elderly patients.

Pharmacokinetics and the Elderly

Physiologic changes associated with the aging process can have profound effects on drug pharmacokinetics and pharmacodynamics.[3] Decreased gastric acidity, gut motility, and absorptive area can affect absorption from the gut, while distribution through the body can be affected by changes in blood flow, body fat, and water ratios.[3] Metabolism and drug clearance can be influenced by decreases in hepatic and renal function so that lower dosages are sufficient to achieve and maintain therapeutic blood plasma levels. The extent to which the changes occur is highly variable between individuals; indeed, older patients show greater variability in blood plasma concentrations than younger patients, making it difficult to generalize about optimal dosage regimens.

Little systematic evidence is available regarding the effect of aging on blood plasma levels of antipsychotics. One study in elderly patients who received haloperidol found no difference in the plasma concentration/dose ratio,[4] whereas another study in patients who received thioridazine found that 8 elderly patients had a serum concentration twice as high as that in 8 younger adults after a single 25-mg dose.[5]

In general, clinical experience suggests that when selecting a dosage regimen for elderly patients, an initial dose 25% to 50% of that for younger patients represents the optimal balance between efficacy and side effects, allowing for gradual upward titration. In the case of quetiapine, there is some suggestion that the function of the cytochrome P450 3A4 (CYP 3A4) isoenzyme, the principal enzyme by which quetiapine is metabolized, may decline with age, necessitating a lower optimal dose.[6] An initial dose of 12.5 to 25 mg daily titrated to 75 to 125 mg daily in older patients has been suggested, although doses up to 800 mg daily have been used.[7,8]

Chronic medical conditions are more common in older patients, and as many as 80% of elderly patients are thought to have at least one chronic disease.[9] Many of the potential side effects of antipsychotic therapy could exacerbate underlying medical conditions; for example, weight gain could exacerbate diabetes or cardiac conditions, potentially leading to increased morbidity and mortality. Polypharmacy is also more common, increasing the potential for adverse reactions as well as drug-drug interactions.

EPS

The nature and treatment of EPS have been discussed elsewhere in this supplement (see Gerlach[10]). Older patients in general appear to be extremely sensitive to EPS, including akathisia, tardive dyskinesia (TD), and parkinsonism. Age itself is an independent risk factor for the development and severity of TD. In a naturalistic survey of 215 inpatients (mean age = 77 years) who received (unspecified) antipsychotics for the treatment of organic psychoses, such as dementia, or psychiatric illness, such as major affective disorder or schizophrenia, the incidence of antipsychotic-induced TD was 31% (95% confidence interval [CI] = 20 to 42) after 43 weeks of cumulative treatment.[11] The incidence of TD appears to be similarly high in outpatients receiving antipsychotic therapy. In a study of 439 middle-aged and elderly patients receiving outpatient and antipsychotic treatment (mainly haloperidol or thioridazine), the incidence of TD was found to be 28.5% after 1 year of treatment, with cumulative rates of 50.1% and 63.1% after 2 and 3 years of therapy, respectively.[12] Elderly patients also appear to be particularly sensitive to the development of the parkinsonian side effects of antipsychotic therapy. Anticholinergic agents can be used to treat such symptoms, but their association with cognitive impairment significantly limits their use in elderly patients.

Acute EPS often resolve after discontinuation of antipsychotic treatment. However, this may not be an option for schizophrenic patients for whom discontinuation of treatment may significantly increase the risk of relapse. A recent review of 66 studies in younger patients (N = 4356) with schizophrenia or schizoaffective disorder found that discontinuation of treatment led to relapse in 53% of patients, compared with 16% of patients who were maintained on treatment.[13] Relapse rates appear to be similar in older patients[14]; therefore, antipsychotics with minimal or no association with EPS, such as the atypical agents, are of considerable benefit.

Atypical antipsychotics as a group have a far lower propensity to cause EPS compared with conventional agents. However, although risperidone and olanzapine are associated with EPS at higher doses in studies involving nonelderly subjects, quetiapine is associated with no more EPS than placebo across all doses in subjects of similar age.[15] Definitive studies of this issue in the elderly have not yet been completed.

A Half Century of Psychosis: A Case Report Describing the Ethical Dilemma of Treating an Elderly Patient With Long-Term Schizophrenia

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Care of the elderly schizophrenic patient can present particular ethical and clinical challenges. This case study illustrates the need for continual review of treatment strategies in elderly patients, as well as highlighting the ethical dilemma advances in the treatment of schizophrenia can create.

Case report. Mr. T, a 73-year-old man, has been in continuous hospital care for 42 years. After numerous moves, he currently resides in a nursing home. His psychiatric history extends to 1947, when he was diagnosed with an anxiety state following an automobile accident. He was first admitted to the hospital in 1949; no diagnosis was recorded, and he was described as depressed and discharged himself after 32 days. Mr. T re-presented in 1956 and has remained in psychiatric care since then. A diagnosis of chronic schizophrenia was made, and he was given a dental clearance 2 months after admission. Dental clearance as a treatment for psychosis is based on the focal sepsis theory that emerged at the turn of the century, although it is no longer regarded as a valid therapeutic approach.

Upon assessment in 1998, Mr. T had no significant medical problems and was taking no other medication. He had no neurologic problems or extrapyramidal signs and was fully mobile with a normal gait. However, Mr. T was fecally incontinent, required regular toileting to maintain urinary continence, would not wash or change his clothes without prompting, and isolated himself for much of the day in a small sitting area separate from the main day room. He only responded to staff he knew well with appropriate monosyllabic answers. He occasionally produced more expansive, but incomprehensible, speech and was observed to turn his head, apparently in response to visual and/or auditory hallucinations.

A review of his recently rediscovered medical notes, which had become lost during his many moves, revealed that Mr. T had not received any aggressive treatment for his mental condition. In 1959, he received chlorpromazine with no benefit (dose and duration not recorded). Flupenthixol decanoate was given as a single dose in 1979, after which he became notably tremulous. No further antipsychotic therapy was given until 1992, when Mr. T received thioridazine, 25 mg twice daily. Although this treatment had no significant impact on his mental state, he continued to receive thioridazine for 5 years.

Quetiapine treatment was initiated in 1998 as monotherapy at 25 mg twice daily. Within a few weeks, staff noticed a difference in Mr. T's behavior as he began to spend more time in the main day room. He also initiated using the toilet himself and was rarely incontinent. The dose was increased to 125 mg twice daily, and he continued to improve. Most notably, he is now able to acknowledge that he is feeling better.

Treatment with quetiapine has begun to resolve Mr. T's schizophrenic symptoms, improving his social functioning and self-care. Continued improvement is expected, although the ethical dilemma of such improvements in an elderly patient with long-term, untreated schizophrenia, is not easily resolved. Relieving the symptoms of schizophrenia and restoring awareness to a patient who has apparently remained oblivious to his surroundings for 50 years could create significant psychological problems in itself. However, is it fair to deny a patient potentially effective treatment? Achieving a balance between the physician's desire to effect a cure and the patient's best interests in such circumstances remains an ethical dilemma that will not be easily resolved as our knowledge of, and treatments for, schizophrenia continue to advance.

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Orthostatic Hypotension

Orthostatic hypotension is a common side effect of a number of medications, including antipsychotics. Blunted postural reflexes and decreased vasoregulatory ability make elderly patients particularly susceptible to orthostatic hypotension, which is a major contributor to the occurrence of falls and subsequent fractures, and even strokes, in older patients. The consequences of such injuries can be severe, leading to functional decline, dependence, and even death. Again, the atypical antipsychotics offer benefits over conventional agents. Although clozapine can cause severe orthostatic hypotension, risperidone, olanzapine, and quetiapine are associated, for the most part, with mild-to-moderate effects. Particular care must be taken to avoid combining medications with the potential to cause orthostatic hypotension. For example, antiparkinsonian agents can also cause orthostatic hypotension, but this can be avoided by prescribing an antipsychotic such as quetiapine, which is not associated with significant motor system disturbance and therefore does not create the need for adjunctive therapy.

Osteoporosis

The conventional antipsychotics are known to cause an elevation in plasma prolactin levels, and this effect has also been associated with the atypical agents risperidone

and olanzapine.[16] The subsequent decrease in levels of gonadotropins and other gonadal hormones consequent to prolactin secretion can potentially lead to a decrease in bone mineral density and osteoporosis although data are not available to establish the significance of this in the elderly.[17] Such decreases in bone mineral density may not be limited to women, who experience the added risk factor of menopause. One study in younger psychiatric patients receiving conventional antipsychotics found that both male and female patients had significant decreases in their bone mineral density.[18] Quetiapine, at all recommended doses, is not associated with elevations in plasma prolactin levels,[19] and less than 0.1% of 2387 patients who received quetiapine in controlled clinical trials in non-elderly subjects reported reproductive or hormonal adverse effects.[20]

Anticholinergic Side Effects

Cholinergic function decreases with age, and the addition of anticholinergic effects associated with a number of antipsychotics (either directly or due to the adjunctive treatment of EPS) can result in serious peripheral and central nervous system side effects. Dry mouth can be particularly troublesome in patients with dentures, whereas the potential exacerbation of glaucoma can lead to impaired sight. More serious effects such as confusion, impaired memory, agitation, and even visual hallucinations may also appear. Anticholinergic side effects are most frequently associated with the low-potency conventional antipsychotics such as chlorpromazine. Among the atypical agents, clozapine has a highly anticholinergic receptor-binding profile and olanzapine somewhat less so. In contrast, risperidone[21] and quetiapine have low levels of anticholinergic activity in vitro and in vivo.

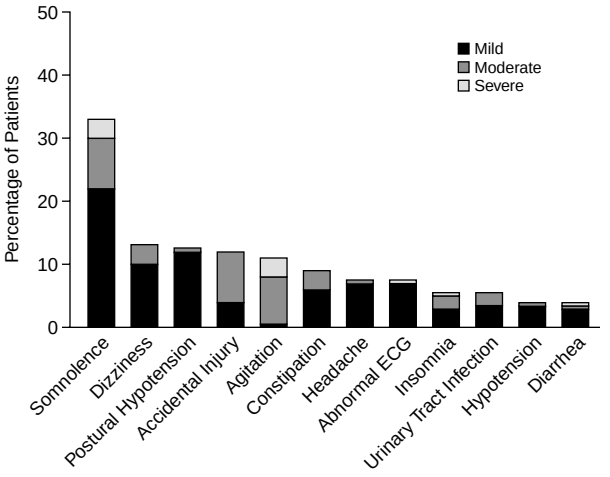
Cognitive Effects

The cognitive effects of schizophrenia and antipsychotic therapy are discussed by Velligan and Miller[1] (this supplement). Cognitive decline occurs frequently in age-associated illness and is also a pathologic feature of schizophrenia. In addition, adjunctive treatment with anticholinergic agents can have a significant impact on cognitive function. The net result of these adverse cognitive effects is increased dependence. It is important, therefore, that pharmacologic treatments for elderly schizophrenic patients do not exacerbate the decline in cognitive function. Atypical antipsychotics, including clozapine, risperidone, and quetiapine, appear to offer a modest, but beneficial, effect on cognitive function compared with conventional agents.[22–24] A recent study with quetiapine suggests that this agent in fact improves cognitive function compared with haloperidol in schizophrenic patients.[1,25]

Cardiovascular Side Effects

Tachycardia, conduction disorders, and arrhythmias have been observed with conventional antipsychotic therapy.[26] Elderly patients may be predisposed to cardiac disorders; thus, the potential for adverse drug interactions is particularly high in such patients and may warrant periodic electrocardiographic (ECG) assessments. Limited data are available in elderly schizophrenic patients regarding the possible associations between the atypical antipsychotics and cardiovascular side effects. Increases in corrected QT interval (QTc) appear to be minimal for clozapine, risperidone, olanzapine, and quetiapine.[9]

Figure 1. Adverse Events Occurring in at Least 5% of Elderly Patients (N = 151) Following Treatment With Quetiapine (up to 800 mg daily) for 12 Weeks[a]



[a]Data from McManus et al.[7] Abbreviation: ECG = electrocardiogram.

QUETIAPINE IN THE TREATMENT OF ELDERLY SCHIZOPHRENIC PATIENTS

The impact of quetiapine on both the positive and negative symptoms of schizophrenia has been demonstrated in a number of controlled comparative clinical trials in younger patients.[27–29]

The efficacy of quetiapine in the treatment of elderly patients with psychotic symptoms (mean age = 76.8 years [range, 62–94 years]) is currently being studied in an ongoing 52-week open-label trial. Preliminary (12-week) results in 151 patients from this open study have shown that quetiapine (up to 800 mg daily, median dose = 100 mg/day) offers considerable benefits in symptomatic relief and has acceptable tolerability.[7] This study included patients with a broad range of psychiatric disorders, including both idiopathic and organic psychoses. Significant improvement in Brief Psychiatric Rating Scale (BPRS) total scores ($p < .0001$) and the Clinical Global Impression-Severity of Illness scale (CGI-S) scores ($p < .01$) were observed from week 2 onward, and 52% of patients showed a clinically significant improvement (defined as ≥ 20% decrease in BPRS score).[7]

Despite the inclusion of patients with Parkinson's disease, who would have been expected to be especially vulnerable to the side effects of treatment, quetiapine was generally well tolerated. Nine patients (6%) experienced EPS, a lower rate than has been observed previously in younger patients who received placebo.[15] All events were mild in intensity except one case of akathisia, which was classified by the patients' doctor as being of moderate intensity. The Simpson-Angus Scale score improved significantly by endpoint ($p < .0001$), no changes were observed in Abnormal Involuntary Movement Scale scores. A small number of patients experienced symptoms consistent with antihistaminic effects (dry mouth, 6 patients; constipation, 12 patients). The most common adverse events were somnolence (48 patients), dizziness (21 patients), and postural hypotension (19 patients; Figure 1). Weight gain was minimal: the mean increase from baseline was 0.78 kg.[7]

Results from the 52-week analysis (N = 184) support these interim findings.[8] Patients received quetiapine (median total daily dose = 138 mg) for, on average, 348 days. The statistically significant improvements in BPRS and CGI-S scores noted at the 12-week analysis were maintained at the study endpoint (BPRS, $p < .0001$; CGI, $p < .0001$), and 49% of patients achieved a clinically significant improvement overall. Quetiapine continued to be well tolerated and was associated with negligible EPS, no clinically important changes in laboratory parameters or ECG rates or intervals, and minimal weight gain.

These results, combined with those from studies in younger patients, including the potential benefits in cognitive function, suggest that quetiapine may offer considerable benefits to elderly patients with psychotic symptoms, in terms of both efficacy and tolerability.

A Case Study

The case study reported by Yorston[30] (this supplement) illustrates the potential efficacy of quetiapine in the treatment of elderly schizophrenic patients. The administration of quetiapine began to resolve the patient's symptoms within weeks, improving his ability to communicate his feelings and to care for himself. Prior to this, the patient had not received adequate treatment for his symptoms resulting from schizophrenia, underlining the need for continual assessment and reevaluation of individual patients.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

REFERENCES

1. Velligan DI, Miller AL. Cognitive dysfunction in schizophrenia and its importance to outcome: the place of atypical antipsychotics in treatment. J Clin Psychiatry 1999;60(suppl 23):25–28
2. Eastham JH, Jeste DV. Treatment of schizophrenia and delusional disorder in the elderly. Eur Arch Psychiatry Clin Neurosci 1997;247:209–218
3. Crome P, Flanagan RJ. Pharmacokinetic studies in elderly people: are they necessary? Clin Pharmacokinet 1994;26:243–247
4. Aoba A, Kakita Y, Yamaguchi N, et al. Absence of age effect on plasma haloperidol neuroleptic levels in psychiatric patients. J Gerontol 1985;40: 303–308
5. Cohen BM, Sommer BR. Metabolism of thioridazine in the elderly. J Clin Psychopharmacol 1988;8:336–339
6. Sweet RA, Pollock BG. New atypical antipsychotics. Experience and utility in the elderly. Drugs Aging 1998;12:115–127
7. McManus DQ, Arvanitis LA, Kowalcyk BB, for the Seroquel Trial 48 Study Group. Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders. J Clin Psychiatry 1999;60:292–298
8. Tariot P, Salzman C, Yeung P, et al. Clinical improvement and tolerability is maintained long-term in elderly patients with psychotic disorders treated with quetiapine. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 19, 1999; Washington, DC. Abstract NR542:219–220
9. Maixner SM, Mellow AM, Tandon R. The efficacy, safety, and tolerability of antipsychotics in the elderly. J Clin Psychiatry 1999;60(suppl 8):29–41
10. Gerlach J. The continuing problem of extrapyramidal symptoms: strategies for avoidance and effective treatment. J Clin Psychiatry 1999;60(suppl 23): 20–24
11. Saltz BL, Woerner MG, Kane JM, et al. Prospective study of tardive dyskinesia incidence in the elderly. J Am Med Assoc 1991;266:2402–2406
12. Jeste DV, Rockwell E, Harris MJ, et al. Conventional vs newer antipsychotics in elderly patients. Am J Geriatr Psychiatry 1999;7:70–76
13. Gilbert PC, Harris MJ, McAdams LA, et al. Neuroleptic withdrawal in schizophrenic patients. Arch Gen Psychiatry 1995;52:173–188
14. Jeste DV, Lacro JP, Gilbert PL, et al. Treatment of late-life schizophrenia with neuroleptics. Schizophr Bull 1993;19:817–830
15. Hellewell JSE, Cameron Hands D, McKellar J. "Seroquel": an effective atypical antipsychotic with no greater EPS than placebo across the full dose range [abstract]. Schizophr Res 1998;29:154
16. Jibson M, Tandon R. New atypical antipsychotic medications J Psychiatr Res 1998;46:8–14
17. Ataya K, Mercado A, Kartagine J, et al. Bone density and reproductive hormones in patients with neuroleptic-induced hyperprolactinemia. Fertil Steril 1988;50:876–881
18. Halbreich U, Rojansky M, Palter S, et al. Decreased bone mineral density in medicated psychiatric patients. Psychosom Med 1995;57:485–491
19. Hamner MB, Arvanitis LA, Miller BG, et al. Plasma prolactin in schizophrenia subjects treated with Seroquel (ICI 204,636). Psychopharmacol Bull 1996;32:107–110
20. Goldstein JM, Cantillon M. Low incidence of reproductive/hormonal side effects with "Seroquel" (quetiapine) is supported by its lack of elevation of plasma prolactin concentrations. In: Proceedings of the 21st Collegium Internationale Neuro-Psychopharmacologicum Congress; July 12–16, 1998; Glasgow, Scotland. 338 Abs PTO7093
21. Schotte A, Janssen PF, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology (Berl) 1996;124:57–73
22. Lee MA, Thompson PA, Meltzer HY. Effects of clozapine on cognitive function in schizophrenia. J Clin Psychiatry 1994;55(9, suppl B):82–87
23. Stip E, Lussier I, Babai M, et al. Seroquel and cognitive improvement in patients with schizophrenia. Biol Psychiatry 1996;40:434–435
24. McGurk SR, Green MF, Wirsching WC, et al. The effects of risperidone vs haloperidol on cognitive functioning in treatment-resistant schizophrenia: the trail making test. CNS Spectrums 1997;2:60–64
25. Velligan DI, Bow-Thomas CC. Executive function in schizophrenia. Sem Clin Neuropsychiatry 1999;4:24–33
26. Maletta GJ. Use of antipsychotic medication in the elderly. Annu Rev Gerontol Geriatr 1984;4:175–220
27. Goldstein JM, Arvanitis LA. ICI 204,636 (Seroquel): a benzothiapine atypical antipsychotic: review of preclinical pharmacology and highlights of phase II clinical trials. CNS Drug Rev 1995;1:50–73
28. Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233–246
29. Peuskens J, Link CGG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand 1997;96:265–273
30. Yorston G. A half century of psychosis: a case report describing the ethical dilemma of treating an elderly patient with long-term schizophrenia. J Clin Psychiatry 1999;60(suppl 23):31