Treatment-Resistant Schizophrenia: Reviewing the Options and Identifying the Way Forward

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Between 20% and 40% of schizophrenic patients are thought to be resistant to conventional antipsychotic therapy, although this may be an underestimate of the scale of the problem. The causes of nonresponsiveness are likely to be multifactorial, and there have been reported associations between refractoriness and neuropsychological impairment, negative symptoms, and abnormal brain morphology. For some patients, treatment resistance may in fact represent an intrinsic part of the schizophrenic illness. Treating the refractory patient should begin with a full, preferably multidisciplinary, review of diagnosis, symptoms, and side effects. Although an increased dose of a conventional antipsychotic agent can be effective for some patients, consideration should be given to reducing the dose and combining treatment with psychosocial management, or switching to one of the newer atypical antipsychotics.
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Despite the proven efficacy of antipsychotic drugs, a substantial proportion (20%–40%) of patients will prove resistant to treatment.[1,2] If the definition of treatment resistance is broadened to encompass social, occupational, and cognitive measures, rather than purely symptoms,[3] then, it has been suggested, the proportion suffering from treatment resistance would increase correspondingly.[4] Moreover, research-based criteria, such as those of Kane,[3] with their emphasis on demonstrable nonresponse to treatments given sequentially, might be expected to result in an underestimation of the scale of the problem, principally by excluding the many patients with incomplete response to treatments.

A CONTINUUM OF TREATMENT RESPONSE

It is easy to assume that treatment-resistant patients represent a discrete and homogenous subgroup; clinical trials, for example, have tended to adopt a categorical basis of classification. However, there is considerable variability within the population of nonresponders, some showing a modest response to a new treatment, others a minimal change, and some a deterioration. The alternative and arguably the more helpful view is that refractoriness to treatment in schizophrenia, rather than representing a discrete category, instead is better viewed as a continuum.[5] This view is in accordance with the clinical perception that the majority of schizophrenic patients do not fall easily into either responder or nonresponder categories, but instead fall onto a dimension of response, from the minority who experience full resolution of symptoms and restoration of normal social and occupational function to those who show minimal if any response to treatment of any sort. The characteristics of and clinical approach to the great many "partial responders" are described more fully in an earlier article in this series.[6]

THE CAUSES OF TREATMENT REFRACTORINESS

We have seen that response to antipsychotic treatment is best viewed as representing a continuum and that poorly responsive patients show considerable clinical heterogeneity. Similarly, the causes of nonresponsiveness are best thought of as multifactorial.

It is often assumed, for example, that refractoriness represents the end result of institutionalization or of some endogenous morbid process. The often reported associations between refractoriness and neuropsychological impairment,[7] negative symptoms,[8] and abnormal brain morphology[9] might provide support for this view. In contrast, however, Lieberman et al.[10,11] demonstrated, in a prospective study, that high levels of treatment resistance were seen in 8 of a group of 70 patients with first-episode schizophrenia. Therefore, in some patients at least, treatment resistance might be best thought of as representing an intrinsic part of the schizophrenic illness.

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The role of antipsychotic medication in determining outcome has received considerable attention. Van Putten et al.[12] and Rifkin et al.,[13] for example, invoked the concept of the therapeutic window, with low antipsychotic plasma levels being ineffective and high levels being associated with symptom exacerbation, perhaps due to increased toxicity. Certainly, some patients improve following reductions in antipsychotic dosage; Van Putten et al.[14] describe a series of such patients. In addition, the studies of very high or "megadose" therapies have provided no support for an enhanced efficacy at very high doses.[15,16]

It is important to bear in mind that a poor psychosocial outcome and protracted hospital admission can result from factors other than nonresponse to medication. Inadequate psychosocial treatment, poor compliance with treatment, and a prior history of violence have all been identified as risk factors for chronic hospitalization.[5] The role of high expressed emotion has been reviewed in detail by Clare and Birchwood.[17] Finally, there are many patients for whom antipsychotic treatments are associated with intolerable side effects and who may equally be regarded as suffering from a treatment-resistant form of illness.

REVIEW OF SYMPTOMS AND RESPONSE TO TREATMENT

When dealing with the treatment-resistant patient, the starting point is a full, preferably multidisciplinary, review of diagnosis, symptoms, and side effects. It is valuable to identify explicitly the target symptoms, together with the improvements in psychosocial function that are to be achieved. The use of rating scales, not just for psychopathology, but also for social function and attitudes to treatment, is to be commended. The target symptoms identified may influence future treatment choices; while conventional agents are effective in ameliorating positive symptoms, they appear to have little effect on the deficit syndrome. In contrast, there is accumulating evidence[18] to support the use of atypical agents for negative symptoms. As indicated in Velligan and Miller's review in this supplement,[19] atypical drugs with minimal burden of extrapyramidal symptoms (EPS) and few anticholinergic properties might be particularly indicated where cognitive problems are prominent.

Anxiety and depressive symptoms are important for many patients in limiting rehabilitation; once again, there is evidence that some of the newer agents may have beneficial effects on mood.[20,21] Antidepressant prescription may be indicated where mood symptoms are marked and persistent.

When reviewing treatment response, it is important to consider whether previous treatments have

The Utility of Quetiapine in a Patient With a History of Poor Response to Previous Treatment

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In the treatment of schizophrenia, antipsychotic agents remain the most effective pharmacologic approach. However, the association of conventional agents with adverse effects and extrapyramidal symptoms (EPS) can compromise patient compliance, leading to, at best, only a partial response to treatment.

Case report. Mr. M, a 36-year-old African American man, has an 18-year history of schizophrenic spectrum disorder and has needed approximately 3 hospitalizations per year since 1980. We report here the dramatic improvement in both his symptoms and compliance following treatment with quetiapine.

Mr. M has carried DSM-IV diagnoses of chronic paranoid schizophrenia, schizoaffective disorder bipolar type, cannabis abuse, and alcohol abuse. His illness has been characterized by a range of positive psychotic symptoms, cognitive disorganization, thought disorders, delusional ideation, and grandiose ideas. He has been observed to respond to both visual and auditory hallucinations. His delusions are often bizarre, and persecutory ideas predominate. His emotional state ranges from guarded, irritable, and suspicious to inappropriate laughter.

Mr. M has been treated with a range of antipsychotics (haloperidol, fluphenazine, chlorpromazine, thioridazine, perphenazine, risperidone, and olanzapine), and other psychoactive medications (lithium, trazodone, clorazepate, zolpidem, propranolol, lorazepam, carbamazepine). Typically, however, these treatments achieve only a partial remission. Moreover, on discharge from the hospital, he is poorly compliant, citing side effects as a major factor, and quickly relapses.

Most recently, Mr. M was admitted to his community hospital after presenting in the emergency room with a further florid relapse of psychosis. His condition was stabilized over several weeks with fluphenazine (25 mg intramuscular injection every 2 weeks), benztropine (4 mg/day), and quetiapine (200 mg/day). Mr. M was subsequently transferred to the Mayview State Hospital for further stabilization. The dose of quetiapine was increased to 300 mg then 500 mg/day over the course of several weeks and intramuscular injections of fluphenazine were discontinued. As quetiapine dosage increased, his hostility and overt psychotic symptoms subsided and his mood lability improved tremendously. EPS and akathisia decreased markedly with discontinuation of fluphenazine and did not reappear during quetiapine treatment.

Mr. M's own perception of his quetiapine treatment has been extremely positive. He reports feeling clearer, more relaxed, and better able to manage his symptoms and has described his response to quetiapine as "the best experienced so far" with minimal side effects. Importantly, Mr. M has been able to talk about the need for long-term compliance with his medication.

This case illustrates the need for patient compliance with treatment if they are to achieve more than a partial remission. The efficacy and tolerability benefits of quetiapine, notably the absence of EPS, may be evident to patients themselves, improving compliance and long-term treatment outcomes.

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been given at sufficient dose and for a long enough period. However, although megadose regimens may be of value in the occasional patient, the evidence in support of this practice is not at all convincing, and large doses are, of course, often associated with greater toxicity. Therefore, it is often valuable to actively reduce doses, particularly if such reduction can be combined with a renewed impetus in psychosocial management. There can be a strong temptation to change therapy prematurely, particularly where there is a risk of violence or disturbed behavior, but, in general, the chosen treatment should be persevered with for at least 6 weeks, and the temptation to "add in" additional drugs, particularly on an "as required" basis, avoided.

MEDICATION ISSUES

Polypharmacy, or the use of multiple antipsychotics, is, in general, to be avoided. There is little, if any, systematic evidence to support this practice and there has, to date, been no convincing demonstration of a robust treatment effect by an adjunctive agent.[22] The use of other drugs can also cause complications: carbamazepine, for example, may reduce blood antipsychotic levels by as much as 50%,[23] while anticholinergic drugs may affect oral absorption of antipsychotics. Despite their widespread use, anticholinergic drugs are probably less benign than is commonly presumed, as their central effects may both exacerbate psychotic symptoms and, through their detrimental effects on cognition, compound disability and limit psychosocial rehabilitation.

Particularly in cases in which patients appear not to have responded to courses of antipsychotics given at moderate doses, or where side effects have been prominent, it is essential to consider the issue of compliance. Plasma levels of antipsychotics may be useful in determining this. Noncompliance is widespread in schizophrenia, occurring in over 45% of patients,[24] and has been shown to predict poor outcome.[25] Fortunately, there have been a number of demonstrations recently that the problem of noncompli-

Long-Term Efficacy and Tolerability of Quetiapine in Treatment-Refractory Schizophrenia: A Case Study

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We report the case of Mr. S, a 58-year-old man with a diagnosis of chronic, therapy-resistant schizophrenia.

Case report. Mr. S was free of any psychiatric problems until the age of 23, when he developed an acute psychiatric episode and received his diagnosis of schizophrenia. His illness was characterized by positive psychotic symptomatology, including persecutory delusions and delusions of reference, auditory and visual hallucinations, and sleep and behavior disturbances. He was initially treated with a phenothiazine antipsychotic to which he responded well. Since then, Mr. S has received a variety of antipsychotic agents including thioridazine, haloperidol, chlorpromazine, and perphenazine, all given at therapeutic doses. Despite this, he has required hospitalization about once a year and has been unable to work for much of his adult life. His paranoid delusions have also persisted, his social functioning has remained poor, and he has continued to experience negative symptoms, affective flattening, and poverty of speech. Increased doses of the above antipsychotics failed to improve Mr. S's mental state, and significant extrapyramidal symptoms (EPS) appeared.

Quetiapine treatment was initiated in 1994 at 100 mg/day and was gradually escalated to 700 mg/day. At first, Mr. S still required benzodiazepine treatment and small doses of an anticholinergic agent to control his EPS, and his prolactin levels were elevated (23.6 ng/mL). A number of rating scales have been used to monitor Mr. S's progress since quetiapine therapy was initiated. After 6 weeks of treatment, he showed significant improvement as measured by the Brief Psychiatric Rating Scale (67% decrease in total score), Scale for the Assessment of Negative Symptoms (28% decrease in total score), Quality of Life Scale (increased from 3 to 41 points), and the Clinical Global Impressions scale (improved by 2 points). His prolactin levels returned to normal (1.3 ng/mL). The EPS, akathisia, and involuntary movements he was experiencing resolved, and his additional medication (benzodiazepines and anticholinergics) was reduced, then finally withdrawn.

To date, Mr. S has been taking quetiapine for 5 years, and he continues to respond well to his treatment, in terms of both efficacy and tolerability. Structured clinical assessments have been conducted at 6-month intervals since initiating quetiapine therapy, and these confirm wide-ranging improvements. His compliance and motivation for treatment have improved drastically. He is now able to function independently in the community and is participating in a psychosocial rehabilitation program.

This case illustrates the efficacy of quetiapine even in patients with long-term treatment-refractory schizophrenia. The case also suggests that the low propensity of quetiapine to induce EPS and elevated prolactin levels, combined with improved quality of life and interpersonal relationships, is likely to result in improved patient compliance and long-term clinical outcomes.

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ance can be reduced by psychological and psychosocial interventions[26,27] and that the benefits of improved compliance are evident over sustained periods.[28]

The case study by Baird (this supplement)[29] illustrates the interaction between subjective experience, compliance, and outcome. It appears that the patient had begun to associate antipsychotic treatment with both limited efficacy and enduring side effects. Side effects, in particular, appear to have been particularly influential in shaping attitudes to treatment and compliance and thereby to have been a major determinant of relapse and outcome. The introduction of quetiapine appears to have allowed this cycle to be broken, resulting in improvements in side effects, symptoms, and function.

Traditionally, it was recommended that treatment-resistant patients should be switched from their existing (conventional) antipsychotic to an alternative conventional agent from a differing chemical class. There is little, if any, systematic evidence to support this practice, and, at the population level, there are no convincing differences

Quetiapine in the Psychosocial Rehabilitation of a Patient With Chronic Schizophrenia

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After a long-term stay in a mental health institution, a return to the community can be a stressful life event and, without adequate pharmacologic and psychosocial support, could even be detrimental for patients with schizophrenia. We report here the case of Mr. J, whose move from hospital to community care was facilitated through the use of the atypical antipsychotic quetiapine and an individualized psychosocial support program.

Case report. Mr. J is in his mid-50s and has an ICD-10 diagnosis of schizophrenia. He has been receiving psychiatric inpatient care for the past 30 years. Mr. J's mental health problems began at around the age of 20 with repeated episodes of agitated depression, which required admission to local mental hospitals and, ultimately, continuous institutional care from the age of 25. When he was initially admitted, he was withdrawn, aggressive, and unable to care for himself. He exhibited persecutory delusions, and episodes of agitation often culminated in assaults on staff or other patients. Since then, his illness has been characterized by unpredictable, often violent behavior, poor social functioning and self-care, and a blunted affect.

Mr. J's symptoms have proved resistant to available pharmacologic agents and electroconvulsive treatment. His condition was stabilized between 1982 and 1996 on a combination of psychotropic medication including 3 classes of oral antipsychotic (droperidol, loxapine, and haloperidol), a depot antipsychotic (zuclopenthixol decanoate), a mood stabilizer, and a benzodiazepine. However, he continued to experience auditory hallucinations and disturbed behavior.

In December 1996, Mr. J was transferred to a novel, supported accommodation scheme with the long-term aim of moving to a smaller group home. Medication was left unchanged during the initial settling-in period, but his mental state deteriorated and incidents of verbal and physical aggression increased. Mr. J's progress was further hampered by persistent psychotic symptoms and extrapyramidal symptoms (EPS) despite an oral antimuscarinic agent (procyclidine) at maximum dosage. The EPS included a parkinsonian tremor, bradykinesia, dystonia, and akathisia. All caused Mr. J significant distress and interfered with most daily activities. A change of depot medication to fluphenazine decanoate (100 mg every 2 weeks) and rationalization of polypharmacy were implemented in late 1997 in an attempt to reduce side effects and improve symptom control.

In March 1998, Mr. J's mental state deteriorated further, and antidepressant medication was initiated, followed by a respite admission to a psychiatric rehabilitation unit. At this time, quetiapine was initiated, after discontinuation of the depot antipsychotic, and cross-titrated against the existing oral antipsychotic to a dose of 250 mg twice daily over a 3-week period. He improved dramatically and was discharged back to his supported accommodation in April 1998. Quetiapine was titrated against his residual psychotic symptoms to a maximum dosage of 375 mg twice daily by June 1998. At this time, he was also prescribed paroxetine (30 mg daily) and lorazepam (1–2 mg as required). Total Health of the Nation Outcome Scales (HoNOS) scores fell from 24 in March 1998 to 7 in July 1998 due to improvements in categories 1, 6, 8, and 9, representing a reduction in core psychotic symptoms and improvement in relationships with others (including reduced hostility and aggression). There followed considerable improvement in positive symptoms and parkinsonism. Mr. J's social interactions improved, and it became possible for him to communicate his subjective experience of his symptoms in greater detail. Although insight into his condition remained partial, Mr. J was able to accept that some of his experiences were symptoms of schizophrenia. This allowed him to begin to engage in cognitive-behavioral therapy.

This case illustrates how the use of an atypical antipsychotic (in this case, quetiapine) can facilitate new initiatives in psychosocial treatment, enabling patients to gain more control of their illness and their lives.

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between the various typical agents in terms of efficacy (for review, see McKenna[30,31]). In addition, Kane et al.[32] showed that fewer than 5% of schizophrenic patients with a documented history of resistance to standard agents showed any response when treated with haloperidol. The case studies by Reznik et al. (this supplement)[33] and Shaw and Brown (this supplement)[34] illustrate all too clearly the common pattern of sequential nonresponse to conventional agents, together with the tendency to use drugs in combination, resulting in a greater burden of side effects for patients.

NOVEL TREATMENTS

Clozapine, the archetypal atypical antipsychotic, is unique in that efficacy in treatment-resistant patients has been shown in a substantial prospective trial, using a well-defined group of patients.[3] Unfortunately, however, the requirement for regular blood monitoring severely limits utility of the drug, while the side effect profile of sedation, salivation, postural hypotension, and reduced seizure threshold dictates that dose increases are made only cautiously and often serve to limit the maximum dose. Moreover, clozapine does not appear to be equally effective in all patients. In the seminal study by Kane et al.,[3] even using the relatively modest criterion of a 20% improvement in the Brief Psychiatric Rating Scale score to define response, only about one third of the clozapine-treated patients could be classified as responding to treatment.

Historically, nonresponders to clozapine might eventually have received treatment with one adjunctive agent or more, used singly or in combination, aimed at enhancing the response seen with antipsychotics alone. These additional therapies, including benzodiazepines, carbamazepine, and other anticonvulsants, lithium, β-blockers, reserpine, and ECT have been reviewed recently by Conley and Buchanan[22] and McKenna.[30,31] There is convincing evidence that some of these therapies may confer additional antipsychotic benefits, in particular carbamazepine, lithium, and ECT, and therefore that individual patients may benefit. However, there is a lack of recent studies using well-defined treatment-resistant populations to guide practice with these treatments.

Fortunately, over recent years, a number of newer atypical antipsychotics have become available. Some of these agents (e.g., olanzapine, quetiapine) share marked structural and pharmacologic similarities with clozapine. Like clozapine, these newer agents share a reduced burden of EPS compared with the older agents; quetiapine, in particular, shows placebo-level EPS, even at the highest doses.[35,36] Understandably, there is great optimism that the proven efficacy of clozapine in treatment-resistant patients will be shared by one or more of these newer agents. To date, there have been no adequately designed studies published that would allow us to resolve this issue with certainty, although there are substantial studies underway with both olanzapine and quetiapine, the results of which will be eagerly awaited. However, since treatment refractoriness lies on a continuum with partial response, the clinician may be reassured by the positive results with quetiapine in a partially responsive population, reported in this supplement by Emsley.[6] The case study by Shaw and Brown (this supplement)[34] illustrates the potential benefit of an atypical agent in chronic treatment-resistant schizophrenia.

Although the atypical antipsychotics are often thought of as a group, it is important to remember that there are important differences between them in both receptor interaction and side effects and potentially, therefore, in efficacy. For example, placebo-level EPS are seen with quetiapine and clozapine, but not with risperidone, which shows substantial EPS at higher doses[37] (the case study by Shaw and Brown,[34] in this issue, illustrates how EPS can limit acceptability of an effective drug, in this case risperidone, and how substitution of an alternative, such as quetiapine, might have benefits in both tolerability and symptom control).

As yet, we know little about whether the lack of response to one atypical would predict nonresponse to others. Therefore, it would be logical to use these drugs in sequence, each for at least 6 weeks, before resorting to combinations of drugs. The case study by Baird (this supplement)[29] describes the progress made by an individual patient once established on quetiapine, despite there having been limited responses to both olanzapine and risperidone.

The case study by Reznik et al. (this supplement)[33] illustrates the substantial and far-reaching improvements that can be seen in treatment-resistant patients following the introduction of a single atypical agent. As is often the case when multiple antipsychotics have been used over lengthy periods, the previous treatments appear to have caused significant EPS and hormonal disturbance; it was only after a few weeks of treatment, when, presumably, previous drugs had been eliminated, that the benign tolerability profile of the new atypical became fully evident.

OPTIMISM FOR THE FUTURE

Finally, it is important that we as clinicians maintain a positive attitude when dealing with treatment-resistant patients. We have a greater influence over our patients' perceptions of their illness and its treatment than we often assume, and now, more than ever, there are grounds for optimism about the future. There can be little justification for therapeutic nihilism, as the range of treatments available to us, both psychological and physical, is greater than ever before. New approaches will continue to appear, and we have only just begun to explore the potential of the newer agents.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), reserpine (Serpasil and others), risperidone (Risperdal).

REFERENCES

1. Prien RF, Cole JO. High-dose chlorpromazine therapy in chronic schizophrenia. Arch Gen Psychiatry. 1968;18:482–495
2. Essock SM, Hargreaves WA, Covell NH, et al. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. Psychopharmacol Bull 1996;32:683–697
3. Kane J, Honigfeld G, Singer J, et al, and The Clozapine Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45:789–796
4. Meltzer HY. Commentary: defining treatment refractoriness in schizophrenia. Schizophr Bull 1992;16:563–565
5. Brenner HD, Dencker SJ, Goldstein MJ, et al. Defining treatment refractoriness in schizophrenia. Schizophr Bull 1990;16:551–561
6. Emsley RA. Partial response to antipsychotic treatment: the patient with enduring symptoms. J Clin Psychiatry 1999;60(suppl 23):10–13
7. Schulz SC, Conley RR, Kahn EM, et al. Nonresponders to neuroleptics: a distinct subtype. In: Schulz SC, Tamminga CA, eds. Schizophrenia Scientific Progress. Oxford, England: Oxford University Press; 1989:341–350
8. Kolakowska T, Williams AO, Jambor K, et al. Schizophrenia with good and poor outcome, III: neurological "soft" signs, cognitive impairment and their clinical significance. Br J Psychiatry 1985;146:348–357
9. Lieberman JA, Jody D, Geisler S, et al. Time course and biological predictors of treatment response in first episode schizophrenia. Arch Gen Psychiatry 1993;50:369–376
10. Lieberman JA, Jody D, Geisler S, et al. Treatment outcome of first-episode schizophrenia. Psychopharmacol Bull 1989;25:92–96
11. Lieberman JA, Alvir JM, Woerner M, et al. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. Schizophr Bull 1992;18:351–371
12. Van Putten T, Marder SR, Wirshing WC, et al. Neuroleptic plasma levels. Schizophr Bull 1991;17:197–216
13. Rifkin A, Doddi S, Karajgi B, et al. Dosage of haloperidol for schizophrenia. Arch Gen Psychiatry 1991;48:166–170
14. Van Putten T, Marder SR, Mintz J, et al. Haloperidol plasma levels and clinical response: a therapeutic relationship. Psychopharmacol Bull 1988; 24:172–175
15. McCreadie RG, Flanagan WL, McKnight J, et al. High dose flupenthixol decanoate in chronic schizophrenia. Br J Psychiatry 1979;135:175–179
16. Bjorndal N, Bjere M, Gerlach J, et al. High dosage haloperidol therapy in chronic schizophrenic patients: a double blind study of clinical response, side effects, serum haloperidol and serum prolactin. Psychopharmacology 1980;67:17–23
17. Clare L, Birchwood M. Social adjustment of patients living at home. In: Mueser KT, Tarrier N, eds. Handbook of Social Functioning in Schizophrenia. New York, NY: Allyn and Bacon; 1998:39–51
18. Goldstein JM. Atypical antipsychotic drugs: beyond acute psychosis, new directions. Emerging Drugs 1999;4:127–151
19. 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
20. Meats P. Quetiapine (Seroquel); an effective and well-tolerated atypical antipsychotic. Int J Psychiatry Clin Pract 1997;1:231–239
21. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998;55:250–258
22. Conley RR, Buchanan RW. Evaluation of treatment resistant schizophrenia. Schizophr Bull 1997;23:663–674
23. Kahn EM, Schulz SC, Perrel JM, et al. Change in haloperidol level due to carbamazepine: a complicating factor in combined medication for schizophrenia. J Clin Psychopharmacol 1990;10:54–57
24. Corrigan PW, Liberman RP, Engel JD. From noncompliance to collaboration in the treatment of schizophrenia. Hosp Community Psychiatry 1990; 41:1203–1211
25. Van Putten T, May PR, Marder SR. Response to antipsychotic medication: the doctor's and the consumer's view. Am J Psychiatry 1984;141:16–19
26. Kemp R, Hayward P, Applewhaite G, et al. Compliance therapy in psychotic patients: a randomised controlled trial. BMJ 1996;312:345–349
27. Goldstein MJ. Psychosocial strategies for maximising the effects of psychotropic medications for schizophrenia and mood disorder. Psychopharmacol Bull 1992;28:237–240
28. Kemp R, Kirov G, Everitt B, et al. Randomised controlled trial of compliance therapy: 18 month follow-up. Br J Psychiatry 1998;172:413–419
29. Baird JW. The utility of quetiapine in a patient with a history of poor response to previous treatment. J Clin Psychiatry 1999;60(suppl 23):15
30. McKenna PJ. Neuroleptic drug treatment. In: Schizophrenia and Related Syndromes. Oxford, England: Oxford Medical Publications; 1994: 196–218
31. McKenna PJ. The management of schizophrenia. In: Schizophrenia and Related Syndromes. Oxford, England: Oxford Medical Publications; 1994: 219–237
32. Kane JM, Aguglia E, Altamura AC, et al. Guidelines for depot antipsychotic treatment in schizophrenia. Eur Neuropsychopharmacol 1998;8: 55–66
33. Reznik I, Benatov R, Sirota P. Long-term efficacy and tolerability of quetiapine in treatment-refractory schizophrenia: a case study. J Clin Psychiatry 1999;60(suppl 23):16
34. Shaw M, Brown R. Quetiapine in the psychosocial rehabilitation of a patient with chronic schizophrenia. J Clin Psychiatry 1999;60(suppl 23): 17
35. 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
36. Hellewell JSE. A review of the tolerability of Seroquel (quetiapine) in the treatment of schizophrenia. In: Advances in Preclinical and Clinical Psychiatry. Excerpta Medica. In press
37. Marder SR, Meibach RI. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835