Conventional versus novel antipsychotics: changing concepts and clinical implications

Gary Remington, MD, PhD, FRCPC; Siow-Ann Chong, MB BS, MMed (Psychiatry)

Remington — Clarke Institute of Psychiatry and Department of Psychiatry, University of Toronto, Toronto, Ont; Chong — Clarke Institute of Psychiatry, and Institute of Mental Health and Woodbridge Hospital, Singapore

Novel antipsychotics represent a significant advance in the treatment of schizophrenia after many years of few developments. The conventional antipsychotics are potent D_2 antagonists, but fail to achieve a response in about 30% of cases. They are also associated with a high rate of extrapyramidal side effects. The greater and broader spectrum of efficacy combined with the reduced short- and long-term side effects of the new drugs such as quetiapine, risperidone, olanzapine and ziprasidone, contribute to a fresh optimism for the pharmacotherapy of schizophrenia. These novel agents are now driving further advances in schizophrenia research through a growing understanding of their pharmacological and clinical profiles. Clozapine, the first novel antipsychotic, has relatively low activity at D_2 receptors, a high affinity for D_4 receptors and a greater 5-HT_2 (serotonin) than D_2 antagonism. Hence, clozapine and other novel antipsychotics can be classified as such by this latter characteristic. However, some of these drugs have D_2 occupancy greater than 60% (the clinical response threshold), while others have a lower D_2 occupancy. The novel antipsychotics according have also been classifed according to their activity on different neurotransmitter systems. While more effective, novel antipsychotics are not a panacea; they have limitations and side effects. In clinical practice, the American Psychiatric Association recommends either a conventional or novel antipsychotic for initial treatment of schizophrenia, whereas Canadian guidelines recommend novel agents. These agents should also be considered for treatment of refractory schizophrenia. Patients whose schizophrenia does not respond to one of these agents may respond to another. Future research should involve longer clinical trials, given the long periods needed to establish efficacy, and should address many remaining questions about the novel agents.

Les neuroleptiques nouveaux représentent un progrès important dans le traitement de la schizophrénie après de nombreuses années de progrès rares. Les neuroleptiques classiques sont de puissants antagonistes D_2, mais ils ne provoquent pas de réponse dans environ 30 % des cas. Ils sont aussi associés à un taux élevé d'effets secondaires extrapyramidaux. Conjuguée aux effets secondaires réduits, à court et à long terme, des nouveaux médicaments comme la quétiapine, la rispéridone, l'olanzapine et la ziprasidone, leur efficacité élargie et accrue contribue à un optimisme nouveau au sujet de la pharmacothérapie de la schizophrénie. À mesure que l'on comprend mieux le profil pharmacologique et clinique de ces agents nouveaux, ces découvertes catalysent d'autres progrès de la recherche sur la schizophrénie. Premier neuroleptique

Correspondence to: Dr. Gary Remington, Schizophrenia Division, Clarke Institute of Psychiatry, Toronto ON M5T 1R8; fax 416 979-6849; gr@sig.clarke-inst.on.ca

Medical subject headings: antipsychotic agents; classification; clozapine; drug therapy; receptors, drug; risperidone; schizophrenia

J Psychiatry Neurosci 1999;24(5):431-41.

Submitted Jan. 13, 1999
Revised May 14, 1999
Accepted May 19, 1999

nouveau, la clozapine a une activité relativement faible face aux récepteurs D_2, une grande affinité pour les récepteurs D_4 et un antagonisme plus important par rapport à 5-HT_2 (sérotonine) qu'à D_2. C'est pourquoi il est possible de classer la clozapine et d'autres neuroleptiques nouveaux comme tels au moyen de cette dernière caractéristique. Certains de ces médicaments occupent toutefois D_2 à plus de 60 % (le seuil de réponse clinique), tandis que d'autres occupent D_2 dans une proportion moindre. Les neuroleptiques nouveaux ont aussi été classés selon leur effet sur différents systèmes neurotransmetteurs. Même s'ils sont plus efficaces, les neuroleptiques nouveaux ne sont pas une panacée : ils ont des limites et des effets secondaires. En pratique clinique, l'American Psychiatric Association recommande un neuroleptique classique ou nouveau comme premier traitement contre la schizophrénie, tandis que les guides de pratique canadiens recommandent l'utilisation d'agents nouveaux, qu'il faudrait aussi envisager pour traiter une schizophrénie réfractaire. Les patients dont la schizophrénie ne répond pas à un de ces agents peuvent réagir à un autre. Les recherches futures devraient comporter des études cliniques de plus longue durée, compte tenu de la longueur des périodes nécessaires pour déterminer l'efficacité des médicaments, et devraient répondre à un grand nombre de questions qui persistent au sujet des agents nouveaux.

Introduction

"Consider your verdict," the King said to the jury.
"Not yet, not yet!" the Rabbit hastily interrupted.
"There's a great deal to come before that!"
— Lewis Carroll, *Alice's Adventures in Wonderland*

After several decades of few changes in the pharmacotherapy of schizophrenia, it is ironic that clinicians in North America now have 4 antipsychotics at their disposal; namely, clozapine, quetiapine, risperidone and olanzapine, with the prospect of additional compounds, such as ziprasidone, entering the market soon. Clinicians involved in the treatment of schizophrenia are being exposed simultaneously to a wealth of information regarding theoretical developments in the field and to data comparing the relative efficacy of new antipsychotics. Therefore, they might best rely on the advice of the White Rabbit and refrain from making absolute conclusions until more information is available. At the same time, however, clinical reality dictates that we must incorporate these new agents into our practice and that decisions must be based on our present understanding. While not an exhaustive overview of the topic, this article reviews recent evidence regarding these new antipsychotics in the context of current thinking and treatment guidelines for schizophrenia.

What is "atypical?"

It is common to hear terms such as "novel," "atypical" and "second-generation" used interchangeably to describe new antipsychotics, including clozapine, quetiapine, risperidone and olanzapine, but what do these terms actually mean? Many sources of information contribute to the development of investigational compounds, including in vitro and in vivo pharmacology, animal behavioural models and clinical trials, each of which propose measures of "atypicality." However, conclusions drawn from preclinical data can be hampered by differences between in vitro and in vivo pharmacology, species differences and limitations of the animal models used.[1,2] Clinical data can be confused by issues related to their design and methodology, as well as by terminology; for example, primary versus secondary negative symptoms and the definition of refractory symptoms.[3,4]

It is not surprising, therefore, that the precise definition of "atypical" in the clinical setting remains unclear.[5–10] Previously, the properties characteristic of clozapine, the prototype atypical antipsychotic, have been used to define the term "atypical." These characteristics include superior efficacy in refractory psychosis compared with other antipsychotics, efficacy in treating both positive and negative symptoms, a decreased liability for inducing acute extrapyramidal side effects (EPS) and tardive dyskinesia (TD), and no induction of prolactin elevation. However, several issues are raised by confining the definition of "atypical" to this profile:

1. Defining "atypical" according to the clinical profile of clozapine leads to bias in favour of clozapine alone.
2. Existing terminology and criteria are questionable. For example, it is still unclear as to whether or not novel antipsychotics can affect enduring primary (deficit) negative symptoms and/or more transient secondary negative symptoms, e.g., depression, neuroleptic-induced EPS, environmental deprivation.[3]

3. Novel compounds may exhibit additional features that distinguish them from conventional agents and warrant the term "atypical," such as not causing weight gain.[10]

There are currently several alternatives for defining the "atypicality" of antipsychotics. First, the definition "atypical" can continue to be based on the characteristics of clozapine; only those antipsychotics that meet *all* the criteria can be classed as "atypical," whereas others may be termed "novel" or "second-generation" antipsychotics. Second, neuroleptics can be classed as "atypical" only if they share some and not all of these characteristics (in a similar way to making a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition), particularly if the criteria are expanded to include other features which are advantageous for any new antipsychotic.[11] Third, the term "atypical" can be abandoned in favour of a more generic term such as "second-generation" antipsychotic, which would allow all new agents to be viewed along a scale for each of the unique features distinguishing them as novel agents.

At the very least, it is important to recognize that there is currently no uniform definition for atypical, and that the various new antipsychotics do not necessarily share the same clinical features, and certainly not the same side effect profiles.

In the present paper, "novel" has been used as the preferred terminology, acknowledging the lack of clear definition currently existing regarding "atypical."

Conventional antipsychotics

Pharmacology

It was a serendipitous observation that chlorpromazine was found to have antipsychotic properties, and thus became the first conventional antipsychotic. Its precise mechanism of action was unclear, however, and it was a number of years before it was established that its action was associated with inhibition of the dopaminergic system.[12] This led to the hypothesis that schizophrenia was caused by hyperdopaminergic activity, specifically in the mesolimbic dopamine system, and the antipsychotic effects of chlorpromazine were subsequently associated with blockade of the dopamine D_2 receptor.[13] Consequently, efforts turned to the development of highly selective D_2 antagonists, and thus potent antipsychotics, such as haloperidol and pimozide.

Clinical properties

Conventional antipsychotics represented the first definitive pharmacotherapy for schizophrenia — they act on the positive and negative symptoms of the disease, being potent antagonists at the D_2 receptor, and have varying serotonergic interactions, ranging from negligible (e.g., haloperidol) to moderate (e.g., chlorpromazine). However, the clinical use of these traditional antipsychotics over several decades has highlighted their practical limitations; they are not a panacea for all patients with schizophrenia, and up to 30% of patients fail to respond adequately to conventional neuroleptic treatment.[14] Moreover, it has become evident that side effects, particularly EPS, occur in as many as 90% of individuals exposed to these drugs.[15]

Inappropriate antipsychotic dosing is now believed to be associated with the induction of these untoward side effects. The shift to high-potency compounds, such as haloperidol, which have a decreased risk of cardiovascular side effects, permitted the doses of neuroleptics to be increased to the point that they were approximately 3.5 times higher than those of low-potency antipsychotics.[16,17] Unfortunately, the diminished risk of cardiovascular side effects with high-potency compounds was paralleled by a marked increase in the risk of EPS. By the late 1980s, lower doses were being advocated, owing to the lack of clinical evidence showing that higher doses led to greater or more rapid resolution of symptoms.[16] More recently, positron emission tomography and clinical data have supported the opinion that doses of haloperidol in the range of 2 to 8 mg equivalents daily are adequate for optimal clinical response.[18–23]

Limitations

The development of conventional antipsychotics has played a critical role in our understanding of schizophrenia and its recognition as an organic illness. Nevertheless, several decades of clinical experience with these compounds and other developments in this field have challenged existing theories and raised various questions. First, highly selective D_2 antagonists were not as effective as had been anticipated based on the unifying hyperdopaminergic model of schizophrenia, suggesting that other receptors or neurotransmitters or both might be involved in the illness. Second, side effects, especially EPS, became characteristic of the use of conventional antipsychotics. Finally, advances in

our knowledge of schizophrenia suggested that various symptom clusters exist; for example, positive, negative and cognitive symptoms, each of which may be mediated by different mechanisms. Taken together, these issues contributed to the development of second-generation antipsychotics.

Novel antipsychotics

Clozapine is the prototypical "atypical" antipsychotic, although it is not a new agent *per se*, having first been synthesized in the 1960s and released for use in the early 1970s. Its withdrawal in most countries shortly thereafter was due to a cluster of unexpected deaths, which were subsequently associated with its ability to induce agranulocytosis.[24] Clozapine was reinstated for clinical use in North America in the early 1990s, based on clinical evidence that it had significant advantages over its conventional counterparts.[25]

Numerous reports have substantiated the claim that clozapine is superior to conventional antipsychotics in the control of positive symptoms, which have proven refractory to conventional antipsychotics.[25–30] Clozapine has also demonstrated superior efficacy in the treatment of negative symptoms, although it is debatable whether this effect is confined to secondary or primary symptoms or deficit symptoms.[25–31] More recent evidence has suggested that clozapine may be superior to its conventional counterparts in controlling the neurocognitive symptoms associated with schizophrenia.[32–34] It is hoped, therefore, that clozapine may be able to halt, or at least delay, the decline in cognition that can occur in a subgroup of patients with schizophrenia.

Finally, the clinical profile of clozapine is indicative of a markedly reduced risk of acute EPS and a minimal risk of TD.[35–37] Moreover, clozapine does not induce sustained hyperprolactinemia, a side effect also associated with conventional antipsychotics, which results clinically in galactorrhea, amenorrhea and sexual dysfunction.[31]

These findings demonstrated the significant advantages of clozapine over conventional antipsychotics, and initiated the search for further compounds that could offer similar benefits without the associated risk of blood dyscrasias.

Pharmacology

The unique clinical properties and pharmacological profile of clozapine challenged existing theories about the biochemical factors mediating schizophrenia. In particular, the relatively low activity of clozapine at the D_2 receptors was corroborated by in vitro and in vivo data, and this encouraged a re-evaluation of the notion that D_2 blockade alone accounts for antipsychotic efficacy.[18,38] Clozapine also exhibited a relatively high affinity for the D_4 receptor, although recent evidence has indicated that selective D_4 antagonists are not effective antipsychotics.[13,39] Thus, if the D_4 receptor is involved in the pathogenesis of schizophrenia, it is through an interaction with either the other receptors or neurotransmitter systems.

Meltzer et al[40,41] postulated that a ratio indicating greater 5-HT_2 versus D_2 antagonism could be used to predict the "atypicality" of antipsychotics, and subsequent compounds were synthesized to achieve this particular profile. In Canada, we now have additional novel compounds, namely risperidone, olanzapine and more recently, quetiapine. Various other agents, such as ziprasidone, are under investigation, and at least one or more of these compounds are expected to be approved for use over the next few years. With each, there have been data to suggest that they have a broader spectrum of clinical activity or an improved side effect profile, particularly from the standpoint of EPS with compared to the conventional agents.

Classification of novel agents

At least 3 models can be used to conceptualize these new "atypical" antipsychotics. The first and "cleanest" model was that suggested by Meltzer et al,[40,41] i.e., these antipsychotics are similar by virtue of their greater 5-HT_2 versus D_2 antagonism. Based on this pharmacological similarity, the model therefore predicts that the novel antipsychotics would be approximately equivalent clinically.

This model has been extended by Kapur and Remington,[42,43] to suggest that while greater 5-HT_2 versus D_2 antagonism may be integral to the atypical features shared by these compounds, the degree of D_2 occupancy is critical in distinguishing these compounds both pharmacologically and clinically. Several of the novel antipsychotics currently available, i.e., risperidone and olanzapine, demonstrate greater than 60% D_2 occupancy at therapeutic doses.[44,45] This is the threshold associated with effective clinical response in compounds that appear to mediate their response through D_2 antagonism.[43,46] It can be argued, therefore, that both risperidone and olanzapine, despite their unique pharmacological properties, induce their antipsychotic effect through D_2

antagonism. In contrast, both clozapine and quetiapine generally display D_2 occupancy below 60% at therapeutic doses; clozapine is characterized by relatively low D_2 but high 5-HT_2 occupancy, whereas quetiapine has both low D_2 (< 60%) and 5-HT_2 (< 80%) occupancy.[46,47]

Finally, the idea that other neurotransmitters may be involved in schizophrenia is supported by evidence indicating that clozapine is pharmacologically rich, leading to the suggestion that "atypicality" is achieved through activity at a number of neurotransmitter systems.[9,48] Gerlach and Peacock,[9] for example, have classified some of the novel agents using this approach. Novel antipsychotics such as risperidone and ziprasidone have serotonergic, dopaminergic and adrenergic antagonism in common, whereas clozapine, quetiapine and olanzapine are grouped together not only because of their action on these systems, but also because of their effects on muscarinic and histaminergic receptors (Table 1).

These models may prove useful in our understanding of the neuropharmacology of schizophrenia, particularly if clinical evidence favours a specific classification system. Currently, there are few published controlled trials comparing the novel antipsychotics.[49–52]

Limitations

Novel antipsychotics undoubtedly offer significant advantages over conventional compounds, particularly because they are associated with fewer EPS than conventional antipsychotics. They are not a panacea for schizophrenia, however, and have their own limitations and unique side effect profiles (Table 2), which, to some extent, can be predicted from their specific binding profiles.[53]

Another limitation is related to the outcome measures and clinical efficacy of novel antipsychotics. Although novel antipsychotics appear to have a broader and more robust spectrum of clinical efficacy for negative, affective and possibly cognitive symptoms than their conventional counterparts, data are not always consistent either between or within studies, when using different scales to assess the same outcome measures. While the interpretation of data may be qualified by dose-dependent differences and improvement in secondary versus primary symptoms, it has been hampered by the numerous tests used to evaluate neurocognition. Indeed, the implication of positive findings in neurocognition tests is unclear. Moreover, success with clozapine in treatment-resistant patients suggests that all new antipsychotics are superior in this respect, but few studies have actually addressed this population of patients. Even with clozapine, a substantial number of patients remain refractory to treatment such that further advances in pharmacotherapy are required.

Finally, the increasing importance of health econom-

Table 1: Classification of novel atypical antipsychotics according to 3 models based on receptor occupancy

Model*	Antipsychotic drug
5-HT_2/D_2 ratio	Clozapine
	Risperidone
	Olanzapine
	Quetiapine
	Ziprasidone
5-HT_2/D_2 threshold	
High 5-HT_2 / High D_2	Risperidone
	Olanzapine
	Ziprasidone (?)
High 5-HT_2 / Low D_2	Clozapine
Low 5-HT_2 / Low D_2	Quetiapine
Multireceptor	
D_2 / 5-HT_2 / α_1	Risperidone
	Ziprasidone
D_2 / 5-HT_2 / α_1 / ACh / Hist	Clozapine
	Olanzapine
	Quetiapine

*ACh = acetycholine
D = dopamine
Hist = histamine
5-HT = 5-hydroxytryptamine (serotonin)

Table 2: Most common side effects of the novel atypical antipsychotics

Antipsychotic	Side effect	Incidence, % of patients
Clozapine	Drowsiness	39
	Hypersalivation	31
	Tachycardia	25
	Dizziness	19
	Constipation	14
Olanzapine	Somnolence	26
	Agitation	23
	Insomnia	20
	Headache	17
	Nervousness	16
Quetiapine	Headache	20
	Somnolence	18
	Drowsiness	10
	Constipation	9
	Postural hypertension	8
Risperidone*	Insomnia	26
	Agitation	22
	EPS	17
	Headache	14
	Anxiety	12

* ≤ 10 mg per day (6- to 8-week controlled clinical trials)

ics means that the costs of using new antipsychotics cannot be overlooked, particularly because these drugs can cost up to 50 times more per year than conventional agents. Medication, however, represents only a small percentage of the calculated total costs for schizophrenia healthcare, and this proportion is more than counterbalanced by savings made in other areas such as inpatient bed days.[54-57] Unfortunately, a "silo mentality" towards the dispensing of health care funding has sometimes prevented a balanced approach to the overall costs of schizophrenia health care.

Implications of antipsychotics in current clinical practice

Initial treatment for schizophrenia

The immediate question clinicians face is the role of novel antipsychotics in the treatment of schizophrenia. The American Psychiatric Association (APA) has established guidelines stating that either conventional or novel neuroleptics are acceptable for the initial treatment of schizophrenia,[58] whereas more recent Canadian guidelines suggest that the preferred choice is a novel antipsychotic.[59] There is at present a paucity of data comparing novel and conventional antipsychotics in first-episode psychosis; those data that do exist are conflicting.[60,61] The difficulty in finding differences in patients with first-episode psychosis may be because this particular population generally responds well to treatment, thereby producing a ceiling effect that masks potential differences between agents.[62] Future studies that employ a broader spectrum of outcome measures to assess neurocognition, affective symptoms, relapse rates and quality of life, may support a distinction between novel and conventional antipsychotics, particularly if they are longer-term studies.[62] However, existing data favour the use of novel antipsychotics, mainly because they are associated with fewer side effects such as EPS.[60,61]

EPS and novel antipsychotics

The decreased risk of EPS with the newer antipsychotics cannot be dismissed lightly.[63-65] While noncompliance is a complex and multifactorial issue, EPS have been linked with neuroleptic-induced dysphoria and noncompliance.[66] Moreover, EPS represent a risk for TD and, while conventional antipsychotics appear to induce structural changes in the CNS that may be associated with TD, these can be reversed by administration of novel agents such as clozapine.[67-71] Evidence also increasingly suggests that failure to achieve early and effective control of psychotic symptoms results in a poorer long-term outcome in these patients than in those in whom these symptoms have been successfully controlled at an early stage.[72-75]

Thus, while data concerning clinical efficacy are limited, evidence does suggest that the use of novel antipsychotics for first-episode psychosis can reduce side effects and treatment discontinuation, which is of critical importance to clinicians trying to effectively control schizophrenia in its earliest stages.

Treatment-resistant psychosis and novel antipsychotics

Clinicians must also consider the alternative antipsychotics available for treating patients who respond poorly to the initial treatment regimen. The success rate in treating patients with a second conventional antipsychotic if the first has failed is not well established; however, it has been shown to range from 25% to 62% for conventional agents and from 35% to 78% for novel agents in patients with chronic and occasionally acute exacerbations of schizophrenia.[66,76-84] A more striking difference is found in studies using a better-defined refractory population, where response rates ranged from 4% to 32% for conventional agents and from 33% to 100% for novel agents.[25,27,28,30,85] However, all but one of these studies employed clozapine as the novel agent;[25,27,28,30] in the one study that used risperidone, there was no significant difference in response rate between risperidone (33%) and haloperidol (24%).[85]

If patients do not respond to treatment with a novel compound, the APA guidelines allow the sequential use of different novel compounds, although again, there are few data directly comparing the novel compounds. Of the small number of controlled, double-blind studies published to date, several compare risperidone and clozapine, but only in terms of their side effects.[49,50,52] Moreover, although Tran et al[51] have shown that olanzapine may be superior to risperidone in terms of side effects and outcome, others have reported clinical comparability between different novel agents.[86] Interestingly, while one study showed clozapine to be efficacious in risperidone nonresponders, this was not the case with risperidone in clozapine nonre-

sponders.[87-89] Case reports have increasingly indicated, though, that with respect to all novel antipsychotics, including clozapine, individuals may respond to another of the newer agents when one has failed.[90-93]

Before leaving this topic, a point should be made regarding the evaluation of the response. An expansion of this concept in schizophrenia outcome research has led to an increase in number of measures, e.g., positive, negative and affective symptoms; neurocognition; and quality of life. Accordingly, studies differ in the measures employed to assess outcome and, at times, the definition of response for a particular variable. Having said this, pharmacological studies evaluating patients with chronic or more refractory psychosis often require improvement of at least 20% in overall scores on measures such as the Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale. In contrast, it is not uncommon to expect improvement of 50% or more for individuals after a first episode of psychosis.

So what options are available to the clinician to facilitate decision-making regarding choice of antipsychotics in treatment-resistant psychosis? First, if a conventional agent used as a first line of treatment has been unsuccessful, a novel rather than another conventional antipsychotic should be tried next. If a novel antipsychotic chosen as a first line of treatment has failed, the clinician can investigate the efficacy of various newer agents, although it is premature to rank the clinical efficacy of these drugs in light of the present lack of data. As with conventional agents, those individuals who have failed to respond to one novel agent may respond to another. In patients who have been treated unsuccessfully with novel agents first, it is questionable as to whether they should be prescribed a conventional agent next before switching to clozapine. Future studies may influence these decisions and provide information as to whether clozapine should be "moved up" on the treatment algorithm in individuals who are treatment-resistant soon after the onset of schizophrenia.

Noncompliance and depot medication

An additional issue concerns the potential benefit of depot antipsychotics in treating nonresponsive patients, since up to 40% of relapses are the result of noncompliance rather than lack of medication efficacy.[94,95] While it might be argued that novel antipsychotics adequately address this issue because of the decreased risk of side effects associated with their use, this may be translated into improved potential compliance. However, noncompliance is a complex issue and involves factors other than side effects alone (Table 3). It is known that improved compliance, as can occur with depot neuroleptic therapy, decreases relapse rates by about 15%.[96] Since no depot formulation is currently available for novel antipsychotics, it may be more appropriate to treat individuals with existing depot neuroleptics. Therefore, after several trials of either conventional or novel antipsychotics, clinicians should investigate a trial of depot neuroleptic therapy in any individual whose lack of response may be due to noncompliance rather than nonresponse. This would at least allow an accurate documentation of noncompliance and a distinction between noncompliance and nonresponse to be made.

Although augmentation strategies have not been adequately addressed here, and the APA guidelines are limited in this respect, further information can be found in earlier, more detailed reviews of this area.[97,98] There is a lack of substantial evidence for any one strategy, although of note is the APA's reference to electroconvulsive therapy for augmentation, which reflects a returning interest in this approach for the treatment of schizophrenia.[99]

Duration of trials with antipsychotics

Finally, the duration of trials with antipsychotics also warrants comment. Generally, trials lasting 4 to 8 weeks are adequate to assess the efficacy of an antipsychotic, although reports involving clozapine have suggested

Table 3: Factors associated with compliance with treatment with novel atypical antipsychotics

Side effects
Level of insight
Social supports
Frustration
Symptom severity
Symptom type
Grandiosity
Negative symptoms
Cognitive disorganization
Age
Substance abuse
Complexity of treatment regimens
Treatment delivery system
Medication cost

trials lasting 3 months or more.[100,101] One reason for this may be that the unique pharmacological profile of clozapine requires a longer interval to establish efficacy. More recently, however, data from a study using risperidone in a similar population (i.e., refractory schizophrenia) have also indicated that a trial of 4 months or more may be advantageous for optimal response.[88] This suggests that patients with treatment-resistant psychosis, many of whom have been ill for a considerable length of time, justify a more extended trial.

Future directions

The development and investigation of various novel antipsychotics has advanced our understanding of schizophrenia considerably, while also raising additional questions. The following highlight a few of the as yet unanswered questions:

1. Are the novel antipsychotics, at least those available currently, clinically equivalent? Will other novel antipsychotics parallel clozapine, the prototype, in such areas as refractory schizophrenia, suicidal behaviour and cost-effectiveness?
2. Will early treatment with novel antipsychotics alter the course of schizophrenia in a superior way to conventional agents?
3. With respect to neurocognitive symptoms:
   (a) Will future studies confirm the preliminary findings that novel antipsychotics can be effective in this area?
   (b) Are all novel antipsychotics equal in this respect?
   (c) Is the extent of the change in these symptoms clinically meaningful?
   (d) Can such an effect alter the neuropsychological decline seen in some individuals with schizophrenia?
4. Can we enhance functional rather than symptomatic recovery with novel antipsychotics, an effect that has proven elusive with conventional agents?
5. Will novel antipsychotics be equally effective in their capacity to diminish risk of TD? Will the activity of these novel antipsychotics at the level of other receptors or neurotransmitter systems (e.g., 5-HT_2) or both attenuate the risk of clinical EPS caused by their antagonism of D_2 receptors?
6. Will clinical evidence corroborate any of the postulated models of the unique clinical profile of novel antipsychotics?
7. Given that even the novel antipsychotics have limited clinical efficacy, what other biological mechanisms may be involved?

Conclusions

Recent events in the pharmacotherapy of schizophrenia parallel those that led to the development of the selective serotonin reuptake inhibitors (SSRIs) and their impact on the field of affective disorders. In having to learn about an entirely new group of agents for the treatment of schizophrenia, clinicians will have to revise their understanding of the illness and recognize that new theories now exist to explain the pathogenesis and pharmacotherapy of schizophrenia, as well as the clinical benefits of novel compounds. As with the SSRIs in the treatment of depression, this new generation of antipsychotics is not a panacea for the treatment of schizophrenia. However, novel antipsychotics do represent a significant advance in a field that has been dormant for decades, inspiring fresh optimism and providing a springboard for further advances. Answers to many of the questions that have arisen in the development and application of these novel agents are critical to the future developments of our understanding and treatment of schizophrenia.

Acknowledgements

The authors would like to acknowledge with appreciation the support of Zeneca Pharma Inc. (Canada) for an unrestricted eduational grant used to prepare this manuscript.

References

1. Kapur S, Zipursky R, Remington G, Jones C, McKay G, Houle S. PET evidence that loxapine is an equipotent blocker of 5-HT_2 and D_2 receptors: implications for the therapeutics of schizophrenia. *Am J Psychiatry* 1997;154(11):1525-9.
2. Casey DE. Extrapyramidal syndromes in non-human primates; typical and atypical neuroleptics. *Psychopharmacol Bull* 1991; 27(1):47-50.
3. Carpenter WT Jr, Heinrichs DW, Wagman AMI. Deficit and non-deficit forms of schizophrenia: the concept. *Am J Psychiatry* 1998;145(5):578-83.
4. Brenner HD, Dencker SJ, Goldstein MJ, Hubbard JW, Keegan DL, Kruger G, et al. Defining treatment refractoriness in schizophrenia. *Schizophr Bull* 1990;16(4):551-61.
5. Holland D, Watanabe MD, Sharma R. Atypical antipsychotics. *Psychiatr Med* 1991;9(4):5-24.

6. Casey DE. What makes a neuroleptic atypical? In: Meltzer HY, editor. *Novel antipsychotic drugs.* New York: Raven Press; 1992. p. 241-51.

7. Lieberman JA. Understanding the mechanism of action of atypical antipsychotic drugs. A review of compounds in use and development. *Br J Psychiatry* 1993;163(Suppl 22):7-18.

8. Kerwin RW. The new atypical antipsychotics. A lack of atypical side effects and new routes in schizophrenia research. *Br J Psychiatry* 1994;164(2):141-8.

9. Gerlach J, Peacock L. New antipsychotics: the present status. *Int Clin Psychopharmacol* 1995;10(Suppl 3):39-48.

10. Waddington JL, O'Callaghan E. What makes an antipsychotic 'atypical'? conserving the definition. *Cent Nerv Sys Drugs* 1997; 7:341-6.

11. Lieberman JA. Atypical antipsychotic drugs as a first-line treatment of schizophrenia: a rationale and hypothesis. *J Clin Psychiatry* 1996;57(Suppl 11):68-71.

12. Carlsson A, Lindqvist M. Effect of chlorpromazine or haloperidol on formulation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol* 1963;20:140-4.

13. Seeman P. Dopamine receptor sequences: therapeutic levels of antipsychotics occupy D_2 receptors, clozapine occupies D_4. *Neuropsychopharmacology* 1992;7(4):261-84.

14. Schmauss C, Emrich HM. Dopamine and the action of opiates: a re-evaluation of the dopamine hypothesis with special consideration of the role of endogenous opioids in the pathogenesis of schizophrenia. *Biol Psychiatry* 1985;20(11):1211-31.

15. Casey DE, Keepers GA. Neuroleptic side effects: acute extrapyramidal syndromes and tardive dyskinesia. In: Casey DE, Vibeke Christensen A, editors. *Psychopharmacology: current trends.* Berlin: Springer; 1988. p. 74-93.

16. Baldessarini RJ, Katz B, Cotton P. Dissimilar dosing with high-potency and low-potency neuroleptics. *Am J Psychiatry* 1984; 141(6):748-52.

17. Baldessarini RJ, Cohen BM, Teicher MH. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 1988;45(4):75-91.

18. Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D_1 and D_2 dopamine receptor occupancy in patients treated with classical antipsychotics and clozapine: relation to extrapyramidal side effects. *Arch Gen Psychiatry* 1992;49(7):538-44.

19. Nordstrom AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, et al. Central D_2-receptor occupancy in relation to antipsychotic drug effects – a double-blind PET study of schizophrenic patients. *Biol Psychiatry* 1993;33(4):227-35.

20. Kapur S, Remington G, Jones C, Wilson A, DaSilva J, Houle S, et al. High levels of dopamine D_2 receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry* 1996; 153(7):948-50.

21. McEvoy JP, Hogarty GE, Steingard S. Optimal dosing of neuroleptic in acute schizophrenia: a controlled study of neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry* 1991;48(8):739-45.

22. Bollini P, Pampallona S, Orza MJ, Adams ME, Chalmers TC. Antipsychotic drugs: is more worse? A meta-analysis of the published randomized control trials. *Psychol Med* 1994;24(2): 307-316.

23. Stone CK, Garve DL, Griffith J, Hirschowitz J, Bennett J. Further evidence of a dose-response threshold for haloperidol in psychosis. *Am J Psychiatry* 1995;152(8):1210-2.

24. Naber D, Hippius H. The European experience with use of clozapine. *Hosp Community Psychiatry* 1990;41(8):886-90.

25. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for treatment-resistant schizophrenia: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;45(9):789-96.

26. Herrera JM, Costa J, Sramek J, Heh C. Clozapine in refractory schizophrenia: preliminary findings. *Schizophr Res* 1988;1(14): 305-6.

27. Conley RR, Schulz CS, Baker RW, Collins JF, Bell JA. Clozapine efficacy in schizophrenic nonresponders. *Psychopharmacol Bull* 1988;24(2):269-73.

28. Breir A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. *Am J Psychiatry* 1994;151(1):20-6.

29. Kumra S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, et al. Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. *Arch Gen Psychiatry* 1996;53(12):1090-7.

30. Rosenheck R, Cramer J, Xu W, Thomas J, Henderson W, Frisman L, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. *N Engl J Med* 1997;337(12):809-15.

31. Pickar D, Owen RR, Litman RE, Konicki PE, Gutierrez R, Rapaport MH. Clinical and biological response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. *Arch Gen Psychiatry* 1992;49(5):343-53.

32. Hagger C, Buckley P, Kenny JT, Friedman L, Ubogy D, Meltzer HY. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry* 1993;34(10):702-12.

33. Hoff AL, Faustman WO, Wieneke M, Espinoza S, Costa M, Wolkowitz O, et al. The effects of clozapine on symptom reduction, neurocognitive function, and clinical management in treatment-refractory state hospital schizophrenic patients. *Neuropsychopharmacology* 1996;15(4):361-9.

34. Fujii DE, Ahmed I, Jokumsen M, Compton JM. The effects of clozapine on cognitive functioning in treatment-resistant schizophrenic patients. *J Neuropsychiatry Clin Neurosci* 1997;9(2):240-5.

35. Juul Povlsen U, Noring U, Fog R, Gerlach J. Tolerability and therapeutic effect of clozapine: a retrospective investigation of 216 patients treated with clozapine for up to 12 years. *Acta Psychiatr Scand* 1985;71(2):176-85.

36. Gerlach J, Peacock L. Motor and mental side effects of clozapine. *J Clin Psychiatry* 1994;55(Suppl B):107-9.

37. Peacock L, Solgaard T, Lublin H, Gerlach J. Clozapine versus typical antipsychotics: a retro- and prospective study of extrapyramidal side effects. *Psychopharmacology* 1996;124(1-2): 188-96.

38. Coward DM. General pharmacology of clozapine. *Br J Psychiatry* 1992;160(Suppl 17):5S-11S.

39. Kramer MS, Last B, Getson A, Reines SA. The effects of a selective D_4 dopamine receptor antagonist (L-745,870) in acutely psychotic patients with schizophrenia. *Arch Gen Psychiatry* 1997;54(6):567-72.

40. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of D-1, D-2 and serotonergic-2 pK_i values. *J Pharmacol Exp Ther* 1989a;251(1):238-46.

41. Meltzer HY, Matsubara S, Lee JC. The ratios of serotonin-2 and dopamine-2 affinities differentiate atypical and typical antipsychotic drugs. *Psychopharmacol Bull* 1989b;25(3):390-2.

42. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry* 1996;153(4):466-76.

43. Kapur S. A new framework for investigating antipsychotic action in humans: lessons from PET imaging. *Mol Psychiatry* 1998;3(2):135-40.

44. Kapur S, Remington G, Zipursky RB, Wilson AA, Houle S. The D_2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. *Life Sci* 1995;57(10):103-7.

45. Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA, et al. 5-HT_2 and D_2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. *Am J Psychiatry* 1988; 155(7):921-8.

46. Nordstrom AL, Farde L, Nyberg S, Karlsson P, Halldin C, Sedvall G. D_1, D_2, and 5-HT_2 receptor occupancy in relation to clozapine serum concentration: a PET study of schizophrenic patients. *Am J Psychiatry* 1995;152(10):1444-9.

47. Gefvert O, Lundberg T, Wieselgren I-M, Hagstrom P, Bergstrom M, Langstrom B, et al. D_2 and 5-HT_{2A} receptor binding of different doses of quetiapine in schizophrenia [presentation]. American College of Neuropsychopharmacology, 36th Annual meeting; 1997 Dec 8-12, Waikola, Hawaii.

48. Waddington JL, Scully PJ, O'Callaghan E. The new antipsychotics and their potential for early intervention in schizophrenia. *Schizophr Res* 1997;28(2-3):207-22.

49. Klieser E, Lehmann E, Kinzler E, Wurthmann C, Heinrich K. Randomized, double-blind, controlled trial of risperidone *versus* clozapine in patients with chronic schizophrenia. *J Clin Psychopharmacol* 1995;15(Suppl 1):45-51.

50. Daniel DG, Goldberg TE, Weinberger DR, Kleinman JE, Pickar D, Lubick LJ, et al. Different side effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia or schizoaffective disorder: a pilot study. *Am J Psychiatry* 1996;153:417-9.

51. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Anderson SW, Beasley C Jr, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol* 1997;17(5):407-18.

52. Bondolfi G, Dufour H, Patris M, May JP, Billeter U, Eap CB, et al. Risperidone versus clozapine in treatment-resistant schizophrenia: a randomized double-blind trial. *Am J Psychiatry* 1998;155(4):499-504.

53. Gillis MC, editor. *Compendium of Pharmaceuticals and Specialties*, 33rd ed. Ottawa: Canadian Pharmaceutical Association; 1998.

54. Revicki DA, Luce BR, Weschler JM, Brown RE, Adler MA. Cost-effectiveness of clozapine in treatment-resistant schizophrenic patients. *Hosp Community Psychiatry* 1990;41(8):850-4.

55. Honigfeld G, Patin J. A two-year clinical and economic follow-up of patients on clozapine. *Hosp Community Psychiatry* 1990; 41(8):882-5.

56. Meltzer HY, Cola P, Way L, Thompson PA, Bastani B, Davies MA, et al. Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. *Am J Psychiatry* 1993;150(11):1630-8.

57. Jonsson D, Walinder J. Cost-effectiveness of clozapine treatment in therapy-refractory schizophrenia. *Acta Psychiatr Scand* 1995;92(3):199-201.

58. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry* 1997; 154(4 Suppl):1S-6S.

59. Working Group for the Canadian Psychiatric Association and the Canadian Alliance for Research on Schizophrenia. Canadian clinical practice guidelines for the treatment of schizophrenia. *Can J Psychiatry;* 43(2 Suppl):25S-43S

60. Emsley RA, McCreadie R, Livingston M, De Smedt G, Lemmens P. Risperidone in the treatment of first-episode patients with schizophreniform disorder: a double-blind multicenter study [presentation]. 8th European Conference of Neuropsychopharmacology; 1995 October; Venice, Italy.

61. Sanger TM, Lieberman JA, Tohen M, Tollefson GD. Olanzapine versus haloperidol in the treatment of first episode psychosis [presentation]. 9th Biennial Workshop on Schizophrenia; 1998 February 7-13; Davos, Switzerland.

62. Lieberman J, Jody D, Geisler S, Vital-Herne J, Alvir JM, Walsleben J, Woerner MG, 1989. Treatment outcome of first episode schizophrenia. *Psychopharmacol Bull* 1989;25(1):92-6.

63. Fleishhacker WW, Linkz CGG, Hurst BC. ICI 204636 ('Seroquel') — a putative new atypical antipsychotic: results from phase III trials. *Schizophr Res* 1996;18(2-3):132.

64. Arvanitis LA, Miller BG, 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(4):233-46.

65. Casey DE. Seroquel (quetiapine): preclinical and clinical findings of a new atypical antipsychotic. *Exp Opin Invest Drugs* 1996;5(8):939-57.

66. Awad AG. Subjective response to antipsychotics in schizophrenia. *Schizophr Bull* 1993;19(3):609-18.

67. Chouinard G, Annable L, Ross-Chouinard A, Mercier P. A 5-year prospective longitudinal study of tardive dyskinesia: factors predicting appearance of new cases. *J Clin Psychopharmacol* 1988;8(4 Suppl):21S-26S.

68. O'Hara P, Brugha TS, Lesage A, Wing J. New findings on tardive dyskinesia in a community sample. *Psychol Med* 1993; 23(2):453-6.

69. Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lerner G, Bogarts B, et al. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *Am*

J Psychiatry 1994;151(10):1430-6.

70. Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW. Changes in caudate volume with neuroleptic treatment. *Lancet* 1994;344:1434.

71. Chakos MH, Lieberman JA, Alvir J, Bilder R, Ashtari M. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. *Lancet* 1995;345:456-7.

72. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. *Schizophr Bull* 1991;17(2):325-51.

73. Loebel AD, Lieberman JA, Alvir JMJ, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry* 1992;149(9):1183-8.

74. Wyatt RJ. Early intervention for schizophrenia: can the course of the illness be altered? *Biol Psychiatry* 1995;38(1):1-3.

75. Scully PJ, Coakley G, Kinsella A, Waddington JL. Psychopathology, executive (frontal) and general cognitive impairment in relation to duration of initially untreated *versus* subsequently treated psychosis in chronic schizophrenia. *Psychol Med* 1997;27(6):1303-10.

76. Borison RL, Pathiraja AP, Diamond BI, Meibach RC. Risperidone: clinical safety and efficacy in schizophrenia. *Psychopharmacol Bull* 1992;28(2):213-8.

77. Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993;13(1):25-40.

78. Hoyberg OJ, Fensbo C, Remvig J, Lingjaerde O, Sloth-Nielsen M, Salvesen I. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. *Acta Psychiatr Scand* 1993;88(6):395-402.

79. Huttunen MO, Piepponen T, Rantanen H, Larmo I, Nyholm R, Raitasuo V. Risperidone versus zuclopenthixol in the treatment of acute schizophrenic episodes: a double-blind parallel-group trial. *Acta Psychiatr Scand* 1995;91(4):271-7.

80. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994;151(6):825-35.

81. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 1995;166(6):712-26.

82. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996;14(27):111-23.

83. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997;154(4):457-65.

84. Peuskens J, Link CG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand* 1997;96(4):265-73.

85. Claus A, Bollen J, De Cuyper H, Eneman M, Malfroid M, Peuskens J, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic in patients: a multicentre double-blind comparative study. *Acta Psychiatr Scand* 1992;85(4):295-305.

86. Fogelson DL, Sternbach H, Payne D. A naturalistic pilot study comparing haloperidol, clozapine, and risperidone in partially responsive chronic schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 1997;17(6):492-4.

87. Cavallaro R, Colombo C, Smeraldi E. A pilot, open study on the treatment of refractory schizophrenia with risperidone and clozapine. *Hum Psychopharmacol* 1995;10(3):231-4.

88. Smith RC, Chua JW, Lipetsker B, Bhattacharyya A. Efficacy of risperidone in reducing positive and negative symptoms in medication-refractory schizophrenia: an open prospective study. *J Clin Psychiatry* 1996;57(10):460-6.

89. Still DJ, Dorson PG, Crismon ML, Pousson C. Effects of switching in patients with treatment-resistant schizophrenia from clozapine to risperidone. *Psychiatr Serv* 1996;47(12):1382-4.

90. Mok H, Yatham LN. Response to clozapine as a predictor of risperidone response in schizophrenia. *Am J Psychiatry* 1994;151(9):1393-4.

91. Lacey RL, Preskorn SH, Jerkovich GS. Is risperidone a substitute for clozapine for patients who do not respond to neuroleptics? *Am J Psychiatry* 1995;152(9):1401.

92. Avnon M, Kunin A. Risperidone response after no clozapine response. *Br J Psychiatry* 1995;167(5):699.

93. Perkins DO, Lieberman JA. Medical complications and selectivity of therapeutic response to atypical antipsychotic drugs. *Am J Psychiatry* 1998;155(2):272-6.

94. Weiden PJ, Olfson M. The cost of relapse in schizophrenia. *Schizophr Bull* 1995;21(3):419-29.

95. Weiden P, Aquila R, Standard J. Atypical antipsychotics and long-term outcome in schizophrenia. *J Clin Psychiatry* 1996;57(Suppl 11):53-60.

96. Glazer WM, Kane JM. Depot neuroleptic therapy: an underutilised option. *J Clin Psychiatry* 1992;53(12):426-33.

97. Christison GW, Kirch DG, Wyatt RJ. When symptoms persist: choosing among alternative somatic treatments in schizophrenia. *Schizophr Bull* 1991;17(2):217-45.

98. Meltzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophr Bull* 1992;18(3):515-42.

99. Fink M, Sackeim HA. Convulsive therapy in schizophrenia? *Schizophr Bull* 1996;22(1):27-39.

100. Meltzer HY. Duration of clozapine trial in neuroleptic-resistant schizophrenia. *Arch Gen Psychiatry* 1989;46:672.

101. Wilson WH. Time required for initial improvement during clozapine treatment of refractory schizophrenia. *Am J Psychiatry* 1996;153(7):951-2.